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INDICATIONS FOR THERAPEUTIC ABORTION*

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Therapeutic abortion is such a popular subject for discussion that it appears every few years on the agenda of meetings of bodies such as the British Medical Association and the Royal Society of Medicine, and is the basis of much writing. Yet opinion and practice in this country, based as they are on the Hippocratic tradition, on ethics dictated by public opinion, and on the Offences against the Person Act (1861), have not changed in principle for at least 100 years. One of the difficulties in assessing the value of therapeutic abortion to the patient, and therefore its indications, is a lack of factual knowledge. Controlled observations are impracticable, and the outcome for the patient if abortion had not been induced in one case, or if it had been induced in a second case, can never be known with certainty. Any conclusions can rarely be more than opinions, and those articles which purport to give facts are inevitably coloured to a greater or less extent by the religious, ethical, and personal convictions of the writer. This communication is no exception.

The destruction of a living embryo offends something fundamental in human nature, and the most scientifically detached gynaecologist cannot fail to approach an operation of therapeutic abortion with an uneasiness which has been variously credited to "primordial revulsion" (Arkle, 1957) and "subtle archaic motives" (Pearce, 1957). Even the onlookers subconsciously rebel, and, as the pregnancy sac is removed, the surgeon "can feel the shudder of the theatre staff" (Nixon, 1957). It is the entry of individual personal feelings, prejudices, and ethical standards which largely accounts for wide variations in the reported frequency of therapeutic abortion. Other important factors are the educational status and financial prosperity of the community from which cases are selected. In New York City, for example, there are, in proportion to live births, five times as many therapeutic abortions in private hospitals as in municipal hospitals (Gebhard *et al.*, 1959). According to the literature, reviewed by Anderson (1957) and Gebhard *et al.* (1959), the incidence of therapeutic abortion in the hospitals in this country and the U.S.A. varies from 1:35 to 1:16,750 of all births.

During the 10 years 1949–58, in private and hospital practice as conducted by me and my assistants in the Liverpool Maternity Hospital, Mill Road Maternity Hospital, and the gynaecological department at the Liverpool Royal Infirmary, therapeutic abortion was performed 63 times. This figure excludes induction of abortion for ectopic pregnancy, hydatidiform mole, missed abortion, and all conditions in which the foetus was dead or abortion inevitable.† There was also, during the same period, an unrecorded number of cases (probably not more than 10) in which abortion was advised by us but refused by the patient. Out of five women known to be in the last category one died six days, and a second 18 months, after delivery; two, including one of those who died, lost their baby.

The series of 63 cases was drawn from a total number of approximately 40,000 new patients, 28,000 of whom were pregnant. This gives an incidence of rather more than 2 therapeutic abortions per 1,000 pregnant women examined. The abortion cases were, however, selected, partly by sifting at general-practitioner level and partly because they included many specifically referred from associated special clinics concerned with cardiac disease, pulmonary tuberculosis, and the like. The most unselected material was seen at Mill Road Maternity Hospital, where, among 18,094 pregnant women examined by my staff, therapeutic abortion was carried out 14 times, four times at the request of a physician in charge of a special clinic. If these four are excluded, the incidence of therapeutic abortion among the ordinary clientele of hospital antenatal clinics serving a poor-class community with inferior general health was 0.7 per 1,000 maternities. If they are included the incidence was 0.8 per 1,000 maternities. According to this personal experience, the need for therapeutic abortion is nowadays probably not higher than 1 per 1,000 pregnancies. Acceptance of this conclusion means that any one general practitioner who, in England and Wales, is unlikely on average to have more than 40 pregnant women in his practice in any one year, can expect to meet an indication for therapeutic abortion only once in 25 years. His problem is not those cases in which termination of pregnancy is justified, but the far more numerous ones in which it is demanded or discussed. The general physician, the chest physician, the cardiologist, and the psychiatrist encounter this problem rather more frequently. Their particular difficulty is that, when pregnancy occurs in one of their patients already embarrassed by some physical or mental defect, their first and natural reaction is to conclude that removal of the pregnancy would simplify the situation. Their concern may even lead them to go so far as to inform the patient that abortion must be induced, without first consulting the gynaecologist who is expected not only to perform the operation but also to accept legal responsibility. The difficulty

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†In two cases the foetus was found to be already dead at the time of hysterotomy, but these are included because the operation was planned in the belief that the pregnancy was alive.

which results if the gynaecologist then takes an opposite view has two basic roots:

1. The specialist in any branch of medicine, though an expert in his field, usually has little first-hand knowledge of how the patient with organic or functional disease reacts to pregnancy and labour. He rarely appreciates the resilience of women, and especially of pregnant women, in the face of stress. How often does a cardiologist see his patients during labour? How many psychiatrists, having expressed an opinion, follow their patients through pregnancy, labour (or therapeutic abortion), and afterwards?

2. It is not enough to decide that pregnancy is likely to have an adverse physical or mental effect in any case; it has to be shown that the continuance of the pregnancy will be more harmful than therapeutic abortion. Here again those specializing in spheres other than obstetrics and gynaecology generally have little concept of the hazards of terminating pregnancy, and tend to think that it means no more than a simple "D and C" as performed for menorrhagia and dysmenorrhoea, or the evacuation of an incomplete abortion. In fact, therapeutic abortion is a potentially dangerous operation, and can, in many circumstances, offer far more risks than pregnancy and labour.

Hazards of Therapeutic Abortion

Physical Ill-effects

The difficulty in safely terminating a secure and live pregnancy is illustrated by the fact that there is no general agreement on the most satisfactory method. Achievement of the objective always means some surgical intervention. In the very early weeks of pregnancy this may involve forcible dilatation or incision of the cervix with piecemeal and blind evacuation of the products of conception. After the tenth week the choice usually lies between abdominal hysterotomy and the insertion into the uterus of some physical or chemical irritant. The dangers involved can be appreciated by studying the results in those countries where abortion is legally and frequently induced for eugenic and humanitarian reasons. This means that in the majority of such cases the operation is performed on women who are physically and mentally fit.

On such material primary mortality rates as high as 1.7 to 3.5 per 1,000 for therapeutic abortion, and 3.5 to 5.5 per 1,000 for combined therapeutic abortion and sterilization are reported from Sweden (Sjövall, 1951; Westman, 1955). In Denmark, the primary mortality for all cases was once 2 per 1,000 (Oram, 1952), but the most recent statistics suggest that the risk is being reduced. Thus, in their own clinic, Berthelsen and Østergaard (1959a) say there were no deaths associated with 1,235 abortions induced during the years 1953–7. Nevertheless, in Denmark as a whole and during the same period, 23,666 therapeutic abortions with 16 fatalities (0.7 per 1,000) were notified to the national health service (Berthelsen and Østergaard, 1959b). In both these recent series the morbidity rates were high, at least 5% when pregnancy was terminated before the 10th week and 15% after the 10th week. In the Danish national series non-fatal but serious illness resulted after 584 out of 18,346 vaginal operations (3.2%); there were 82 cases of perforation of the uterus, and 122 cases of salpingitis, peritonitis, and septicaemia. In addition, 113 cases of non-fatal serious complications followed 5,320 abdominal hysterotomies (2.1%).

Here, then, is the picture when abortion is carried out on relatively healthy women; what is the outcome when the woman is judged to be so ill as to be incapable of tolerating pregnancy? Women suffering from cardiac, respiratory, and renal incompetence are obvious surgical risks, and when therapeutic abortion is restricted mainly to their type of patient a primary mortality rate of 1% is not unlikely. In fact, among the 63 cases reported here there were no fatalities, but one woman came near to death from pulmonary embolism. Five patients in all became seriously ill (embolism two; ileus one; wound breakdown two), and many took several weeks to recover.

The hazards to life and health are not confined to the immediate post-operative period. Many women whose pregnancy is terminated without apparent complication suffer subclinical infection which renders them permanently sterile. According to Gebhard *et al.* (1959), this risk is often exaggerated, and they quote from the European literature to show that the incidence of sterility is not higher than 1 or 2%. Gynaecologists dealing with cases of infertility are nevertheless aware that it is quite common to see women suffering from tubal obstruction after induced abortion. If this happens when a first pregnancy is interrupted for a non-recurrent indication, such as rubella or a fleeting psychological upset, the situation is tragic.

The type of risk incurred with therapeutic abortion varies not only with the general health of a patient but also with the duration of her pregnancy and the method of its termination. The Danish figures suggest that, whereas abdominal hysterotomy is more often fatal (mostly from embolism), vaginal operations such as curettage, with or without the previous injection of an abortifacient paste, are more often accompanied by non-fatal serious illness due to injury, haemorrhage, and infection. In our series the methods used for therapeutic abortion were:

Dilatation and curettage	1 case
Laminaria tents followed by curettage ..	1 ,,
Abdominal hysterectomy	2 cases
Abdominal hysterotomy	59 ,,

The abdominal route was chosen in nearly all cases because: (*a*) The indication for therapeutic abortion often called for sterilization as well. Tubal resection was performed in all except five women treated by hysterotomy. (*b*) Late diagnosis of pregnancy, accompanied by the need for careful consideration and consultation, meant that only four pregnancies were less than 10 weeks in duration when interrupted. Vaginal operations for terminating relatively advanced pregnancies are notoriously fraught with danger. (*c*) Abortifacient pastes, though possibly having a place, are unpopular in this country because they nearly always have to be followed by curettage, and because their use is not uncommonly complicated by haemorrhage, infection, and general systemic catastrophes (Weilerstein, 1944).

Psychological Ill-effects

Women are so constituted that, even though not wishing to have another child, they generally regret losing one which is already developing in the uterus. If, as in the case of deliberately induced abortion, they themselves play a part in the decision to sacrifice the embryo, they are liable to have lifelong regrets. When women are mentally unstable, and when the indication for therapeutic abortion is more flimsy, as is likely when psychiatric and social factors enter the picture, their peace of mind may be permanently shattered. There is evidence, quoted by Pearce (1957) and Martin (1958), that termination of pregnancy in such circumstances leaves 25 to 59% of the women with remorse and

feelings of guilt. In other circumstances the figure may not be so high, but it is nevertheless significant. Gebhard *et al.* (1959) found evidence of prolonged psychiatric trauma in 9% of a sample of American women who had had abortion induced therapeutically or criminally.

Indications for Therapeutic Abortion

According to English law and its interpretation by the courts, it may not be unlawful to interrupt a pregnancy which would otherwise, in the opinion of the medical attendant, constitute a threat to the life of the woman or which would make her a "physical or mental wreck." The opinion must be honest though not necessarily correct. This implies a wide variety of possible reasons for therapeutic abortion.

Indications for Therapeutic Abortion

Indication	1949–53	1954–8	Total
Heart disease	12	9	21
Pulmonary tuberculosis	10	1	11
Chronic hypertension and allied disease	4	6	10
Renal disease and incompetence	2	4	6
Previous carcinoma mammae	—	4	4
Psychoses and neuroses	3	1	4
Pulmonary incompetence	—	1	1
Carcinoma cervicis	—	1	1
Placenta praevia	—	1	1
Potential foetal abnormality	—	4	4
	31	32	63

The Table shows the main indication present in each of the 63 cases under review. Often more than one factor was present. Thus, one of the cases classified as having a psychiatric indication concerned a 7-gravida, aged 35, who was suffering from "depressive psychosis and neurasthenia," a condition which made it difficult to care for her large family and which was being made worse by the prospect of having still one more child to rear. In addition, however, the patient had had one kidney previously removed for pyonephrosis, and her social and domestic circumstances were of the poorest.

Economic and social factors are never in themselves legally and ethically acceptable as justifying therapeutic abortion in this country, yet, because of their impact on health and disease, they cannot always be disregarded as secondary factors. A patient with severe valvular disease of the heart may well tolerate a first pregnancy when she has no responsibilities which interfere with her having adequate rest, and when her social circumstances are good. A similar degree of cardiac embarrassment occurring in a woman who cannot rest because of having three small children to manage unaided in an unsatisfactory home might, however, constitute an urgent indication for therapeutic abortion. In the past, allied considerations often determined interruption of early pregnancy because of pulmonary tuberculosis. Even after it became generally recognized that this disease is not usually made worse by pregnancy (Robinson, 1931; Stewart and Simmonds, 1947), the immediate institution of the best treatment available often demanded termination of the pregnancy.

Heart Disease

In the area from which this series of cases is drawn, heart disease, generally of rheumatic origin, is common. It remains, as shown during the last five years of the period under review, the leading indication for therapeutic abortion, and this despite a progressive improvement in the general health of the population and despite the developments in cardiac surgery. Indeed, in two out of the last nine cases, valvotomy had previously been performed, but the improvement in cardiac function had proved to be only temporary.

Heart disease is a leading cause of death of pregnant women. Out of 1,410 analysed maternal deaths occurring in England and Wales during the three years 1952–4, 316 were caused by "associated diseases," and cardiac lesions account for 121 of these (Ministry of Health, 1957). The exact place of therapeutic abortion in the treatment of heart disease complicated by pregnancy is difficult to compute, but most obstetricians would probably agree with Sutherland *et al.* (1955) that it is at present indicated in approximately 1% of cases.

Because of the difficulty of foretelling how well an untried heart will tolerate pregnancy, and because the patient can have proper rest and care, therapeutic abortion is rarely indicated in a primigravida suffering from a cardiac disability. This does not mean that the first pregnancy is not potentially dangerous; indeed, approximately 50% of the 121 deaths from heart disease mentioned above occurred among primigravidae. However, even if therapeutic abortion were considered medically desirable most women with cardiac disability would insist on their right to attempt at least one pregnancy. In our series there was only one case in which a first pregnancy was terminated, and this patient was desperately ill and suffering from auricular fibrillation. A second patient with heart disease had previously had one abortion only, and her pregnancy was interrupted only after advice given by three independent cardiologists from two cities. Of the multigravidae, five had fibrillation at the onset of pregnancy and nine had a clear history of heart failure in a previous pregnancy or earlier in the pregnancy under consideration. The remainder showed varying degrees of cardiac embarrassment. It is here relevant to emphasize the long-accepted rule that therapeutic abortion is dangerous when heart failure is present. Its indication is a past history of failure, with subsequent recovery of reasonable efficiency.

Pulmonary Tuberculosis

The introduction of efficient antibiotic therapy for pulmonary tuberculosis quickly altered the place of therapeutic abortion in cases of this disease. The figures in the Table merely illustrate what must be a general experience. They show that out of a total of 11 operations for this indication, only one was performed in the last five years. In that case, pregnancy was terminated not so much for active phthisis as for the fact that one lung was already completely collapsed and the patient suffered considerable respiratory embarrassment. The present-day infrequency of the need for therapeutic abortion for pulmonary tuberculosis is emphasized by the Joint Paediatric and Obstetric Committee of the Joint Tuberculosis Council (1958), and, *according to this committee*, the only circumstances which may constitute an indication are: (1) a serious impairment of pulmonary function by the disease; (2) a patient's adverse psychiatric reaction to the prospect of pregnancy in association with phthisis; and (3) the inability of a multiparous woman to undertake the care of still one more child without breakdown in the control of her disease.

Pulmonary Incompetence

Whereas the last two of the above indications are debatable and not necessarily acceptable, the first is one

which deserves attention. Until recently, pulmonary insufficiency was barely recognized as an indication for therapeutic abortion. The advent of radical lung surgery, however, has introduced a new problem for the obstetricians. Most women can tolerate pregnancy well despite removal of one lung (Williams, 1957), but if they have less than the equivalent of one lung the further embarrassment of respiration caused by late pregnancy and labour can be fatal. This type of problem is seen not only as a result of surgery and of extensive bilateral disease. It also arises in cases of severe kyphoscoliosis affecting the mid-thoracic spine (Dewhurst, 1953). It was this type of deformity, complicated by bronchiectasis, which determined therapeutic abortion in the one case mentioned in this series. It may be added that during the period under review there were, in one of the hospitals from which this series is drawn, two maternal deaths* from cardio-respiratory failure which resulted from previous pneumonectomy in one case and dorsal kyphoscoliosis in the other. Another patient, with widespread bilateral active tuberculosis and very little pulmonary reserve (vital capacity 1,300 ml.), who refused therapeutic abortion, only just survived the respiratory stress of the late pregnancy and labour.

It is difficult to assess pulmonary function and reserve. Safe labour is said to require a vital capacity of at least 1,500 ml., but, according to Williams (1957), clinical observation is a better guide than any such mathematical calculation.

Chronic Hypertension

The reaction of the hypertensive woman to pregnancy is again a matter difficult to predict. Many physicians and obstetricians take a gloomy view of the association, yet, as noted by nearly all speakers at a recent symposium on the subject (Morris and Browne, 1958), it is remarkable how many women start pregnancy with a systolic pressure of more than 160 mm. Hg and a diastolic pressure of more than 90–100 mm. Hg and produce a live healthy baby without any serious mishap or permanent deterioration in their condition. Others, on the other hand, often with a lesser degree of hypertension, may be at serious risk, and so may their babies. In our cases the decision to terminate pregnancy was determined not by the particular height of the blood-pressure but by the past obstetrical history. Therapeutic abortion was mostly reserved for those women whose condition had reacted adversely in past pregnancies and in whom the hypertension appeared to have been the cause of previous antepartum haemorrhage or recurrent abortion and stillbirth.

Renal Incompetence

A history of nephrectomy was not accepted as an indication for therapeutic abortion provided that the one kidney showed evidence of good function. The patients classified as suffering from renal incompetence had lesions such as bilateral hydronephrosis, bilateral resistant pyelonephritis, chronic nephritis with hypertension and nitrogen retention, and tuberculosis of one remaining kidney.

Certain women with chronic nephritis tolerate pregnancy surprisingly well, and, without shortening their life-span, have the satisfaction of producing well-developed healthy babies. They are generally those whose renal disease is not accompanied by hypertension or who do not develop hypertension before the thirtieth week of pregnancy (Wilson, in Morris and Browne, 1958). The immediate prognosis is often better than is generally realized, and may not be much improved by interrupting the pregnancy. In nephritis more than any other disease the question arises, If pregnancy kills, will abortion save ? Two cases seen in recent years illustrate the problem.

A primigravida with normal blood-pressure was found, at the twelfth week of pregnancy, to have some form of chronic nephritis. The physician strongly advised termination of the pregnancy; the patient, supported by the obstetrician, refused to accept the advice. Despite some deterioration in her condition towards the end of pregnancy, this woman secured the baby which she desired. The mother's life was not shortened; it was made happy for two years. Thereafter a baby was left motherless.

The second patient, also primigravid, was known to suffer from bilateral renal hypoplasia with renal rickets and azotaemia. Her life hung by a thread even before pregnancy. Both physician and obstetrician recommended therapeutic abortion, but the patient refused to agree. The baby died *in utero* at the thirty-third week of pregnancy, and the mother died six hours after an easy premature labour. Would therapeutic abortion have done more than fill this woman's last few remaining months of life with remorse ?

Present or Past History of Cancer

Since it became recognized that certain cancers, especially those of the breast, are hormone-dependent and therefore likely to be stimulated by the steroids circulating during pregnancy, the presence or past history of malignant disease is regarded as a possible indication for therapeutic abortion. Cancer of the breast, uterus, and skin certainly tends to grow rapidly during pregnancy, but whether this is due to hormone and vascular changes, or whether it merely reflects the youth of the patient, remains uncertain. During the period studied abortion was induced four times because of a past history of carcinoma mammae, but, at the request of the patient, one pregnancy was allowed to proceed in similar circumstances. A second patient with untreated cancer also went to term. The fact that neither of these women came to obvious harm illustrates that cancer does not inevitably get worse or recur during pregnancy, and is not always a clear indication for therapeutic abortion. Thompson (1954) described a consecutive series of 10 cases in which malignant disease of various types had previously been treated and none suffered ill effects from pregnancy. Ten patients subjected to vulvectomy for carcinoma of the vulva have, in recent years, survived subsequent pregnancy without recurrence of the growth (A. A. Gemmell, 1959, personal communication).

Obstetrical Indications

It is noteworthy that among the 63 cases listed there was only one in which a disease specifically related to pregnancy called for therapeutic abortion. This was an unusual example of placenta praevia in which recurrent and uncontrollable bleeding ultimately necessitated abdominal hysterotomy. In the past, obstetrical indications for inducing abortion were many and

*In a near-by hospital and within the last year another woman, previously subjected to pneumonectomy, died from pulmonary insufficiency in late pregnancy.

varied; there was a time when even contracted pelvis was accepted as an indication. Whitehouse (1932) reported that 52 out of a series of 352 (14%) therapeutic abortions were performed because of hyperemesis gravidarum. So changed is the face of medicine that pregnancy has not once been terminated for this condition in my unit since 1942. This and other abnormalities of pregnancy and labour, while still remaining an occasional indication for therapeutic abortion, can nearly always be treated successfully by other means.

Psychiatric Indications

After surveying world opinion and practice, Robinson (1933) long ago showed that therapeutic abortion is rarely justified for frank psychoses, even those which begin during pregnancy. But since the court ruling in the case of *Rex v. Bourne* in 1938, and with the modern emphasis on psychological medicine, many pregnancies have been terminated for personality disorders: so many that there is widespread fear that "psychiatric indications" are sometimes abused to support the termination of unwanted pregnancies. And if psychiatrists find that gynaecologists often resist their requests to carry out therapeutic abortion, the explanation is that they themselves are not agreed that such requests are justified. This was well illustrated at a meeting of the Psychiatric Section of the Royal Society of Medicine in London in February, 1957, a meeting which the *British Medical Journal* (1957) reported as being "distinguished by the complete lack of agreement."

Some psychiatrists take the view that psychoses, or even the history of such during and after a previous pregnancy, rarely if ever call for therapeutic abortion; equally eminent authorities say that, whereas neuroses never justify terminating pregnancy, certain psychoses may do so. The literature (reviewed by Pearce, 1957; Anderson, 1957; and Arkle, 1957) abounds with opinions, and sometimes figures, in support of diametrically opposed views. Because of differing views and beliefs among psychiatrists and obstetricians, and because the acute anxiety state, possibly accompanied by a threat of suicide, induced by an unwanted pregnancy is regarded as significant by one physician and not by another, psychiatric disorders comprise 40% of the indications for therapeutic abortion in one hospital and 0% in another. Nixon (1957) reported 509 cases in which pregnancy was terminated during 19 years (1938–57) at University College Hospital, London. A psychiatric indication was present in 39%. The comparable figure from St. Mary's Hospital, Manchester (Anderson, 1957), was 12.5%, wheras in the small group reported here it was 4 out of 63 cases (6%).

Anderson (1957) reported on 49 pregnant women with psychological disorders. Seventeen had abortion induced, and 11 of these were followed up; only one (the victim of rape) was obviously benefited. Of the 32 cases in which the pregnancy was allowed to progress, 24 were available for adequate study. Pregnancy went to term in 19 of these women, and 12 suffered no further psychological upset; in the remainder the mental state showed no significant improvement or deterioration, though Anderson comments that therapeutic abortion might have helped three of them. Arkle (1957) described 22 cases of psychiatric disorders in association with pregnancy, and none came to harm through not having abortion induced.

If all the evidence is taken into consideration it is difficult not to conclude that few neurotic or psychotic women are ever benefited by termination of pregnancy and that these are difficult to select. Even a clear past history of puerperal insanity on one or more occasions is not an indication for therapeutic abortion, partly on psychiatric grounds (Ekblad, 1955; Martin, 1958), and partly because this disorder is just as likely to follow abortion as delivery at term (Polonio and Figueiredo, 1955; White *et al.*, 1957). Sometimes the medical attendant cannot help worrying lest a refusal to induce abortion will result in a woman carrying out her threat to commit suicide. It is an aspect of the problem on which records appear to be scarce, but, such as there are, they suggest that it is rare for such a threat to be executed. The woman who takes her life because of an unwanted pregnancy is most often one who has not taken medical advice.

Therapeutic Abortion for Potential Foetal Abnormality

The Committee on Medical Aspects of Abortion (1936), appointed by the British Medical Association to consider this question, issued a report which is remarkable for the following statement: "Whilst under existing conditions reasons based on eugenic considerations are generally regarded by medical men as falling outside the scope of therapeutic abortion, the committee believes that there are certain cases of this class which constitute justifiable indications . . . when there is reasonable certainty that serious disease will be transmitted to the child." The examples given include hereditary blood disorders, certified mental deficiency in both parents or in one parent and one previous child of the union, and certified mental deficiency in two previous offspring. This conclusion was reached despite the fact that the Law did not, and does not, recognize eugenic indications for inducing abortion; and it is of interest that the Council of the British Medical Association did no more than regard "the report as a contribution of great practical value" and hoped that it would receive "careful attention."

To-day the main interest in what might be regarded as eugenic aspects of therapeutic abortion is not concerned with inherited mental disorders so much as with foetal injury and disease resulting from adverse agents operating during early intrauterine life. In Denmark, abortion is already being induced when a pregnant woman has inadvertently been exposed to *x* rays. Hammer-Jacobsen (1959) reported 11 such cases and expressed the view that when a woman less than 16 weeks pregnant is exposed to more than 10 r therapeutic abortion is always indicated; when the dose is between 1 and 10 r the operation may or may not be permissible; when the exposure is less than 1 r the foetal risk is such as not to justify terminating pregnancy. Despite a widespread scare about radiation hazards, this attitude has fortunately not yet developed in this country. Here the adverse agents acting on the foetus which cause most concern are maternal virus infections and maternal antibodies to foetal blood factors.

With regard to virus infections other than rubella it was at one time suggested that they subjected the foetus less than 12 weeks old to a 20% risk of malformation (Grönvall and Selander, 1948; Kaye *et al.*, 1953). More carefully controlled observations (Hill *et al.*, 1958; Siegel and Greenberg, 1959; Caughey, 1959; Hesseltine, 1959) have so far failed

to confirm this, and, for the present, it must be concluded that there is no evidence to show that diseases such as measles, chicken-pox, herpes zoster, mumps, scarlet fever, poliomyelitis, and infective hepatitis significantly distort foetal development, even when contracted by the mother early in pregnancy. The position in regard to influenza is uncertain.* The risk of rubella, however, is real; the only difficulty is to assess its extent and whether it justifies therapeutic abortion in individual cases.

When a foetus is exposed to the rubella virus before the twelfth week it may be killed and aborted. If not, the chance of its eyes, ears, brain, or heart being malformed was initially put at 80%—100% for the first two months and 50% for the third month (Gregg, 1945, 1946; Swan *et al.*, 1943, 1946). This estimate was based on a retrospective study of babies born to mothers during a virulent epidemic of rubella amongst a susceptible community in Australia. Because of these and similar reports many women contracting rubella in early pregnancy have been treated by therapeutic abortion (Wesselhoeft, 1949; Greenberg *et al.*, 1957), and this practice has seriously interfered with the conduct of controlled prospective statistical studies. Another difficulty encountered in such studies is the possibility of variations in risk according to time, place, and community — variations which may reflect differences in virulence of the infection on the one hand and host susceptibility on the other. There is also the uncertainty of the diagnosis of rubella in the mother and of deafness in the young baby. To make matters worse it is possible (Lundström, 1952) that unrecognizable viraemia in a mother immunized by an attack of rubella in earlier life can sometimes be just as dangerous to the foetus as can obvious disease in a susceptible woman.

In so far as any firm conclusions on sublethal effects are possible, the most recent reports from this country (*Lancet*, 1957; Hill *et al.*, 1958; Jackson and Fisch, 1958), from Canada (Oxorn, 1959), from Eire (Coffey and Jessop, 1959), from the U.S.A. (Greenberg *et al.*, 1957), and even from Australia (Pitt, 1959) suggest that: (1) Rubella contracted after the twelfth week† of pregnancy is virtually harmless to the foetus. By that time the basic development of vulnerable organs is complete. (2) When rubella is contracted before the twelfth week the overall risk of foetal malformation is between 10 and 30%, with an average of 20%. This danger may be as high as 50% during the first month, falling to 25% in the second and to 10–15% in the third.

This background and these figures do not permit the general conclusion, as is suggested by Bell (1959), that therapeutic abortion should be induced in every case in which a woman acquires rubella during the first three months of pregnancy. They do, however, suggest a need to consider this operation in individual cases, the nature of the advice offered being ultimately decided by the circumstances of the particular case—the duration of pregnancy, the woman's age, parity, fertility, and the like. Unfortunately, the severity of the clinical manifestation of rubella in any woman is an unreliable guide; the foetus can be affected by viraemia which produces negligible clinical manifestations.

Even when two or more medical opinions are in favour, and when the potential parents agree, there is at first sight no legal justification for therapeutic abortion on account of a rubella hazard to the foetus. The operation only becomes acceptable by showing that the prospect of foetal malformation is causing the expectant mother so much worry that her health is being adversely affected. The pregnancy is thus interrupted on a maternal psychiatric indication rather than in the interests of the foetus. A similar approach is reasonable when it is impossible to allay the fears of the outcome of pregnancy in a woman who already has given birth to two or more physically or mentally abnormal children. In the present series there were four cases in which therapeutic abortion was carried out because of an unfavourable maternal reaction to a high expectation of foetal abnormality. In one the cause of the worry was rubella contracted at the fifth week of pregnancy. In a second the mother had already had three babies, all apparently normal, but all dying within 24 hours of birth for a reason which could not be determined despite the most careful investigation. When contraception failed at the age of 43 years, the patient was so distressed at the idea of having still one more heart-rending experience that the pregnancy was terminated and she was sterilized.

Rhesus incompatibility prompted therapeutic abortion in the remaining two cases. Both women had had two or more affected stillborn babies, and their husbands were homozygous rhesus-positive. In this sort of circumstance the hazard to the mother is not only psychological but can be physical, a fact which is not always appreciated. The risk to maternal health and life arises mainly if the foetus reacts to iso-immunization by becoming hydropic. When this happens there is a 50% chance of severe pre-eclampsia, and, even without this, a high chance of abruptio placentae (Scott, 1958; Jeffcoate and Scott, 1959). The development of hypofibrinogenaemia at the time of delivery is another complication of iso-immunization.

There can be no general rule, but in certain cases, in which the past history and haematological studies suggest that it is almost certain that the foetus will later be fatally affected, induction of abortion may well save the mother's life and health. This is illustrated by the following case.

A rhesus-negative woman, aged 31, married to a homozygous rhesus-positive man, had had five previous babies and one abortion. The last three of the babies were stillborn or died immediately after birth, one being hydropic. Despite careful antenatal supervision this woman sustained abruptio placentae at the twenty-sixth week of her seventh pregnancy. The foetus died *in utero*, and the subsequent premature labour was complicated by severe and persistent post-partum haemorrhage associated with afibrinogenaemia. This near-tragedy, the probability of which was foreseen, could almost certainly have been avoided by therapeutic abortion. This was advised in early pregnancy but was refused by the patient on religious grounds.

Changing Indications for Induction of Abortion

The indications for inducing abortion shown by our experience do not constitute a complete list of possibilities, but they do illustrate that the circumstances

*The possible adverse effect of influenza on the foetus is discussed in recent papers by Victoria Coffey and W. J. E. Jessop (*Lancet*, 1959, **2**, 935) and by M. J. Pleydell (*Brit. med. J.*, 1960, **1**, 309).

†Though it is usual to speak in terms of weeks of *pregnancy*, this and subsequent figures refer to weeks of *amenorrhoea*. This means that the duration of pregnancy is approximately two weeks less.

justifying therapeutic abortion are for ever changing with the advance of medical knowledge. The number of therapeutic abortions performed in each of the two successive five-year periods was the same but the indications were altered. Thus pulmonary tuberculosis virtually disappeared, and in its place appeared other conditions such as malignant disease and potential foetal injury. Comparable lists from other sources might show a swing towards psychiatric indications. The emphasis must also vary with the general health of a community and the geographical incidence of diseases such as rheumatic fever.

It is not long since chorea gravidarum, a past history of difficult labour, lymphadenoma, ulcerative colitis, diabetes mellitus, syphilis, adrenal insufficiency, leukaemia, purpura, epilepsy, otosclerosis, disseminated sclerosis, and many other conditions were acceptable indications for therapeutic abortion. Save in some very special circumstances, none is admissible to-day. And what of to-morrow? Who can say which physical or mental disturbances, at present regarded as being adversely affected by pregnancy, will become amenable to treatment; what hitherto unsuspected impacts of pregnancy on health will be discovered; and what factors governing foetal malformation will come to light? Already the induction of abortion has become more "prophylactic" than "therapeutic." Except for conditions such as hyperemesis gravidarum, there is seldom any hope that by arresting a pregnancy a woman's mental or physical disability will be improved. The operation is nowadays mostly performed with a view to preventing the onset of complications or further deterioration in the primary disease. In this respect not only does the effect of late pregnancy and labour enter into consideration but sometimes even the remote effect of caring for the child after its birth.

Strict adherence to truly medical indications means that the place of therapeutic abortion is shrinking rather than expanding (Rosen, 1954). In practice, and because of misplaced sympathy, pressure from colleagues who may see only one side of the problem, and kindred considerations, it is sometimes tempting to modify personal criteria in assessing a particular case. To make an exception, however, nearly always leads to embarrassing consequences. The induction of abortion on flimsy grounds in one case inevitably results in a demand for further operations for equally doubtful indications. These may come from relatives and friends of the first patient, and sometimes from the patient herself. For if a woman finds it easy to get rid of an unwanted pregnancy she is less careful to avoid another. In Sweden, 38% of women subjected to abortion without sterilization conceive again (mostly unintentionally) within two to four years (Ekblad, 1955). In Japan, 50% of women are pregnant again within 18 months (Gebhard *et al.*, 1959). Such experiences deserve serious consideration by those who would broaden the scope of therapeutic abortion to control population and to include humanitarian and eugenic indications.

It may be that public opinion and medical ethics in this country will some day so change as to result in the legalization of abortion for eugenic reasons. So long as the present attitude obtains, however, new legislation which aimed to define more exactly the circumstances in which abortion is justifiable could be in the worst interests of both patient and doctor. Rapidly occurring developments in medical knowledge might result in its becoming quickly outmoded. The British Medical Association Committee on Medical Aspects of Abortion (1936) and the Interdepartmental Committee on Abortion (1939) advocated not legal definitions of the indications for abortion but a modification of the law to the extent that it was made positively rather than negatively clear that abortion is not always illegal. It was argued then, as it has been since, that the present situation leads to women being deprived of what is in the interests of their health because their medical adviser fears the legal consequences of terminating pregnancy. But I have never heard of a specific case in which such a fear has operated when the medical indications were clear. Nor is it likely to happen, because the present characteristically British legal position provides for the greatest flexibility of opinion and for changes in opinion as medicine advances.

The present law is so strict as to control effectively criminal abortion, yet no doctor need fear its consequences if, after proper consultation with colleagues, he terminates a pregnancy which he honestly believes is causing or is likely to cause significant harm to the physical or mental well-being of his patient. "The essence of the offence is the guilty intent" (Riddell, 1927), and it would seem that one of the best ways to remove any doubt about motive in any case is to make it a rule never under any circumstances to accept a fee or other reward. This applies not only to those performing therapeutic abortion but also to those concerned in the consultations which should precede a decision to undertake such an operation.

The Patient's View

There can be no generalizations about the place of therapeutic abortion. The need for the operation has to be judged separately for each case, judged against a background of medical knowledge but in the light of the special circumstances of that case. When it is decided that there are no medical grounds for terminating an unwanted pregnancy, it is important to warn the patient against attempting to interfere with the pregnancy herself and against resorting to illicit practitioners. That there is a real chance that a woman will adopt these measures is shown by the figures of Anderson (1957) and by the experience of most gynaecologists. It is more likely among the married than the unmarried, and always involves danger to life and health.

When in a particular case there seems to be a medical reason for considering therapeutic abortion, the doctor from whom the patient first seeks advice, no matter whether he be general practitioner, surgeon, physician, or gynaecologist, is wise not to mention the possibility to her lest he prejudice the position. A second and possibly third opinion (including that of the person who is expected to perform the operation) should be obtained, and only when there is professional agreement that abortion is indicated should the matter be discussed with the patient and her husband. The ultimate decision then rests with them. "We have no right or duty to do more than put before wife and husband the relevant facts as we know them, and advise what we think to be the lesser evil" (Batten, 1939).

Many women, often those without special religious scruples, will refuse therapeutic abortion despite the strongest medical advice in favour. They willingly accept any risk to satisfy maternal instinct. The multigravida can console herself that, by sacrificing one

pregnancy, she is preserving her life and health for the better care of her children already born. The primigravida, however, who consents to the destruction of her pregnancy may have no consolation other than a few more years of life, which, being childless, are to her not worth having. If there is a hope of children in the future, when her health has improved, she may agree. When there is no such hope, then her refusal to accept technical advice, if difficult for the male mind to understand, may be both correct and wise. It may cost the medical attendant constant work and worry; it may even result in the spoiling of his statistics for maternity work. It nevertheless illustrates a woman's sense of values, her courage, and her loyalty to her sex.

Summary

Though the practice of therapeutic abortion varies widely in frequency from one hospital to another, a personal experience of 63 cases during 10 years suggests that the need for the operation does not now arise more often than once in every 1,000 pregnancies.

Though the underlying principles governing a decision remain unchanged, the actual indications for terminating pregnancy alter rapidly with advancing medical knowledge. A relatively new indication is pulmonary insufficiency.

Each case needs to be judged separately according to the special circumstances of that case. Any one disease cannot be said to be always an indication for therapeutic abortion.

In making a decision the hazards of therapeutic abortion need to be weighed against those of the continuance of pregnancy. The gynaecologist who is expected to perform the operation should therefore always be one of those consulted before the procedure is suggested to the patient.

The final decision rests with the patient and her husband.

Certain indications for therapeutic abortion are discussed, and it is noted that inherited taints, and diseases such as rubella which threaten the health of the foetus, are only acceptable legally when it can be shown that worry over potential foetal abnormality is adversely affecting the mother's health. Rhesus incompatibility can, however, be dangerous to the mother as well as to the foetus.

Psychiatric indications are easily abused to justify the removal of an unwanted pregnancy.

Induction of abortion nowadays rarely offers hope of improvement or cure of the patient's disease; it generally aims to do no more than prevent deterioration of the mother's condition, and is therefore more often prophylactic than therapeutic.

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Chiropody is one of a group of services which are supplementary to the medical profession, and the opportunities it offers as a career for young persons about to leave school are set out in *The Chiropodist*, a revised booklet in the *Choice of Careers* series published by the Central Youth Employment Executive. The booklet points out that foot troubles have become relatively common because of developments in urban and industrial civilization, and also from the wearing of unsuitable boots or shoes. For a long time the demand for treatment was met by those who had acquired their knowledge and skill from family traditions or apprenticeship, but eventually the need for proper standards of training and practice was recognized. Details of the day-to-day work of a chiropodist, both in and out of the surgery, are given, together with information about the equipment used, the techniques for making special appliances, and openings and salaries in a growing profession which offers increasing scope as people realize the benefits to be derived from treatment. Candidates for training in chiropody must have received a good general education. The training course, as approved by the Minister of Health and the Secretary of State for Scotland, for employment in the National Health Service lasts three years. A list of the schools at which this training is provided is included as an appendix to the booklet. (No. 61, H.M.S.O., price 6d. net.)

THE METABOLISM OF STRONTIUM IN CHILDREN

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The continued rise in the accumulated fall-out of strontium-90 (Libby, 1956; Stewart *et al.*, 1957; Eisenbud, 1959) has prompted several estimates of its rate of transfer from the food-chain to the skeleton of man (Comar *et al.*, 1957a; Bryant *et al.*, 1958; Eckelmann *et al.*, 1958; Kulp *et al.*, 1959). The retention of radioactive strontium in man has also been studied, and the results obtained have been compared with those for calcium, to which it is closely related chemically (Langham and Anderson, 1957; Comar *et al.*, 1957b; Laszlo and Spencer, 1958).

The rate of increase in skeletal calcium has been shown to be most rapid in early infancy and between the ages of 8 and 18 years (Mitchell *et al.*, 1945). Experimental work on the absorption of dietary calcium in children has also shown that it is highest in these age-groups (Duckworth and Warnock, 1942; Widdowson, 1947; Beal, 1954). Since strontium, like calcium, is absorbed from the gastro-intestinal tract and deposited in the skeleton, it is to be inferred that the increase in body strontium would be greatest for these age-groups. No direct information is available, however, on the dietary turnover of strontium in children or the excretion of strontium that follows known oral doses.

In the present experiments the daily urinary and faecal excretion of strontium and calcium has been measured in four children between the ages of 4¾ and 14½ years, over an initial period of seven or eight consecutive days immediately before receiving an oral dose of about 100 mg. of strontium (as strontium chloride). After the dose the daily urine and faecal excretion of strontium and calcium was estimated for 12 to 18 days and the net retention of the dose deduced. The results obtained have been compared with the excretion of an oral dose of strontium by adults from this unit (Harrison *et al.*, 1955).

Method

The children (three sons and a daughter of members of this unit and all unrelated) were on normal diets. Urine was collected over 24-hour periods, and after the volume had been recorded a known aliquot (about 10 ml.) was made up to 50 ml. with distilled water and set aside for the estimation of calcium. The remainder was treated with ammonium oxalate at about neutral *p*H, and after warming and standing for about one hour the solids were separated by centrifuging and the supernatant was discarded. The residue was dissolved in a minimum volume of strong nitric acid and the strontium precipitated as strontium nitrate by the addition of fuming nitric acid (Harrison and Raymond, 1955). After separating the insoluble nitrate precipitate by centrifuging, it was dissolved and made up to a volume of 25 ml.

Faeces were air-dried and subsequently ashed at about 600° C. for about 14 hours. The resultant ash was dissolved in warm 4N hydrochloric acid and any insoluble material (silica and carbon) removed by centrifuging. A known aliquot (about 1% of the total) was removed for calcium estimation. The subsequent treatment of the remainder was exactly similar to that described for urine.

Calcium estimations were made on a Unicam SP900 flame-spectrophotometer by an additive standard method. Strontium was determined on the same instrument by a similar method (Harrison, 1958).

The single dose of strontium chloride (containing 100 mg. of strontium in 25 ml. of distilled water) was taken at breakfast-time on the seventh or eighth day of the experimental period.

Results

The results of the separate experiments are shown in Tables I to IV. The days preceding that on which

TABLE I.—*Urinary and Faecal Excretions of Strontium and Calcium in S. R. W. (Boy age 4 years 10 months). Dose, 99.5 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
–7	0·056	50	—	—
–6	0·048	36	1·19	1·21
–5	0·045	35	1·33	0·91
–4	0·032	30	—	—
–3	0·059	46	0·76	0·59
–2	0·033	27	—	—
–1	0·051	43	1·05	0·76
0	1·14	48	0·51	0·21
1	0·90	28	60·9	0·52
2	0·51	40	—	—
3	0·37	62	21·2	0·63
4	0·136	42	—	—
5	0·293	68	—	—
6	0·268	73	2·29	1·61
7	0·162	60	—	—
8	0·207	81	1·61	0·88
9	0·087	49	—	—
10	0·186	67	2·04	1·06
11	0·115	50	0·92	0·56
12	0·124	55	—	—
13	0·175	80	1·45	1·20
14	0·144	80	—	—
15	0·121	60	1·45	1·18
16	0·103	71	—	—
Total 0–16	5·04	1,014	92·4	7·85

TABLE II.—*Urinary and Faecal Excretions of Strontium and Calcium in M. A. L. (Girl aged 9 years 9 months). Dose 99.5 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
–8	0·062	82	2·91	1·96
–7	0·077	95	—	—
–6	0·122	96	2·68	1·35
–5	0·175	79	—	—
–4	0·065	90	—	—
–3	0·073	65	2·34	1·61
–2	0·132	128	—	—
–1	0·128	103	2·11	1·23
0	1·33	90	1·54	0·78
1	0·485	60	54·65	0·93
2	0·750	129	—	—
3	0·326	106	17·75	1·25
4	0·520	133	2·94	0·57
5	0·208	89	2·13	1·08
6	0·309	134	1·30	0·57
7	0·116	90	—	—
8	0·191	86	3·14	1·21
9	0·147	73	—	—
10	0·038	41	1·77	1·42
11	0·112	100	—	—
12	0·169	120	2·47	0·88
13	0·076	85	1·73	0·74
14	0·067	61	1·94	1·16
15	0·109	93	—	—
16	0·042	62	1·71	0·91
17	0·088	87	2·04	0·88
Total 0–17	5·08	1,639	95·11	12·38

TABLE III.—*Urinary and Faecal Excretions of Strontium and Calcium in A. S. H. (Boy) At Age 13 years 1 month. Dose 93 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
	At age 13 years 1 month. Dose 93 mg. of Sr on day 0			
−7	0·097	81	5·24	2·43
−6	0·188	121	5·35	1·81
−5	0·063	97	1·4	0·56
−4	0·075	50	4·40	1·61
−3	0·166	123	4·83	2·10
−2	0·107	82	2·97	1·41
−1	0·066	53	—	—
0	0·405	54	—	—
1	0·684	120	—	—
2	0·364	91	29·1	1·26
3	0·529	126	42·2	1·87
4	0·408	151	—	—
5	0·236	107	9·7	1·73
6	0·228	86	—	—
7	0·348	139	—	—
8	0·183	78	6·65	3·09
9	0·142	63	—	—
10	0·234	134	—	—
11	0·131	82	7·13	2·04
12	0·175	101	—	—
13	0·192	104	—	—
14	0·172	96	4·90	2·45
Total 0–14	4·43	1,532	99·7	12·44
	At age 14 years 4 months. Dose 100 mg. of Sr on day 0			
−8	0·053	113	—	—
−7	0·071	100	3·80	1·82
−6	0·115	178	—	—
−5			—	—
−4	0·084	43	9·55	3·89
−3	0·126	45	—	—
−2	0·152	102	5·48	2·04
−1	0·140	82	—	—
0	0·520	93	—	—
1	0·689	96	40·1	2·68
2	0·288	64	—	—
3	0·206	70	54·6	2·44
4	0·196	42	—	—
5	0·226	92	7·3	2·38
6	0·154	71	—	—
7	0·104	46	—	—
8	0·198	81	5·91	3·14
9	0·156	55	—	—
10	0·151	88	2·72	1·38
11	0·089	41	2·44	1·51
12	0·088	43	3·81	2·63
13	0·137	42	—	—
Total 0–13	3·20	924	116·9	16·16

the dose of strontium was taken (day 0) are denoted by a negative sign. Denoting the mean values of the ratio of strontium to calcium in the faeces and urine in the pre-dose period by $F\frac{Sr}{Ca}$ and $U\frac{Sr}{Ca}$, the respective excretions of dietary strontium during the experimental period may be taken as

$$F\frac{Sr}{Ca}\Sigma F_1 Ca \text{ and } U\frac{Sr}{Ca}\Sigma U_1 Ca$$

where $\Sigma F_1 Ca$ and $\Sigma U_1 Ca$ represent the total calcium excreted by the respective routes after taking the dose. The strontium excreted over the experimental period will then be given by

$$\Sigma F_1 Sr - F\frac{Sr}{Ca}\Sigma F_1 Ca + \Sigma U_1 Sr - U\frac{Sr}{Ca}\Sigma U_1 Ca \quad (1)$$

where $\Sigma F_1 Sr$, $\Sigma U_1 Sr$ represent the total strontium excreted in the faeces and urine respectively in the post-dose period.

Such treatment of the results corrects for day-to-day variations in the amount of food eaten by the children provided that the strontium:calcium ratio of the diet remains unchanged before and after the dose is taken.

Table V gives the results for the mean daily urinary and faecal excretion of strontium and calcium before the oral dose as well as the mean ratio of strontium to calcium excreted by the separate routes. Table VI summarizes the results obtained for the excretion and retention of the oral dose together with the means and their standard errors. For comparison the corresponding results for adults are shown in each of these tables. The latter were derived from previous observations by Harrison *et al.* (1955). To make the two sets of results comparable, those for the adults are given for a period of 16 days after the dose. The calculation of the net excretion, as in the case of the children, was made by the use of formula 1.

The results for R.M. (Table VI), a boy 14½ years old whose growth rate was less and whose physical development was more mature than that of the other children, are exceptional in that his urinary excretion of the dose was intermediate between that of the other children and the adults, while his faecal excretion was very nearly the mean of that obtained for the adults. Presumably R.M. was in the transitional stage between child and adult, when it is known that the excretion of calcium shows a pronounced change (Widdowson, 1947). The results for R.M. are therefore excluded from the means for the other children.

It will be seen from Table VI that the general pattern of excretion of an oral dose of strontium differed markedly in children and adults. Thus there is a pronounced decrease in the percentage of the dose which is excreted in the urine and a smaller but clearly significant increase in the percentage excreted in the

TABLE IV.—*Urinary and Faecal Excretions of Strontium and Calcium in R.M. (Boy Aged 14 years 6 months). Dose 100 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
−8	—	—	3·90	1·49
−7	0·317	267	0·33	0·17
−6	0·215	175	5·40	1·88
−5	0·265	129	2·28	1·04
−4	0·347	177	4·87	2·60
−3	0·292	191	—	—
−2	0·292	189	—	—
−1	0·334	266	7·15	2·82
0	4·43	249	—	—
1	1·79	152	2·65	0·90
2	1·59	211	19·96	1·88
3	0·85	198	12·25	0·34
4	0·60	156	40·40	2·86
5	0·67	43	4·0	1·55
6	0·64	212	—	—
7	0·39	171	—	—
8	0·66	342	—	—
9	0·45	240	5·41	2·37
10	0·31	170	2·80	1·04
11	0·37	230	3·85	1·22
Total 0–11	12·75	2,374	91·3	12·16

TABLE V.—*Comparison of the Excretion of Calcium and Strontium by Children and Adults on a Normal Diet*

	Sex	Age yr. mths	Urinary Excretion			Faecal Excretion		
			Sr (mg.)	Ca (g.)	Sr/Ca ×10³	Sr (mg.)	Ca (g.)	Sr/Ca ×10³
Children:								
S.R.W.	M	4 10	0·049	0·039	1·25	0·62	0·50	1·24
M.A.L.	F	9 9	0·104	0·093	1·12	1·26	0·77	1·63
A.S.H. (1)	M	13 1	0·109	0·087	1·25	3·46	1·42	2·44
,, (2)	M	14 4	0·093	0·083	1·12	2·35	0·97	2·42
R.M.	M	14 6	0·293	0·199	1·46	2·99	1·25	2·39
Adults:								
H.C.C.	F	29	0·271	0·246	1·10	2·97	1·49	1·99
A.H.	F	31	0·152	0·153	1·00	1·61	0·90	1·79
R.H.M.	M	40	0·333	0·386	0·86	2·32	1·13	2·05
J.F.L.	M	45	0·435	0·500	0·87	1·58	0·56	2·82

TABLE VI.—*Percentage Excretion and Retention of an Oral Dose of Strontium*

	Period, Days	Excretion			Retention
		Urinary	Faecal	Total	
Children:					
S.R.W.	17	3·8	83·0	86·8	13·2
M.A.L.	18	3·3	75·3	78·6	21·4
A.S.H. (1)	15	2·7	74·3	77·0	23·0
,, (2)	14	2·2	78·0	80·2	19·8
Mean ..	16	3·0±0·4	77·7±1·9	80·7±2·2	19·3±2·2
R.M. ..	12	9·1	62·9	72·0	28·0
Adults:					
R.H.M.	16	20·5	64·8	85·3	14·7
G.E.H.	16	15·8	63·5	79·3	20·7
H.C.C.	16	19·1	66·2	85·3	14·7
Mean ..	16	18·5±1·4	64·8±0·8	83·3±2·0	16·7±2·0

faeces for the children as compared with the adults. However, the percentage of the dose retained after about 16 days (equal to the dose minus the total excretion) is not significantly different for the children and the adults. If the faecal excretion were to be taken to represent the unabsorbed fraction of the dose, the absorption of strontium from the gastro-intestinal tract in the adults would be about 1.6 times greater than in the children.

Table VII shows values which have been derived for the mean daily dietary intake and the mean daily increment in strontium and calcium deposited in the skeleton. The daily increments in skeletal calcium (column 5) were obtained from results given by Mitchell *et al.* (1945). Obviously these are approximate means which apply to standard children on an adequate calcium diet. Bryant *et al.* (1959) have determined the ratio of strontium to calcium in selected bones from children of various ages. This ratio is approximately constant (280 μg.Sr/g.Ca) over the age-group 5 to 16 years. The daily increment in skeletal calcium multiplied by the ratio 280 μg.Sr/g.Ca was used to give an estimate of the mean daily increment in skeletal strontium for the various children (column 4). The mean daily intake of strontium and calcium (columns 6 and 7) was derived as the sum of the mean daily excretion and the daily increment in skeletal strontium or calcium.

Columns 8 and 9 give the ratio of the skeletal increment to the dietary intake for strontium and calcium, while column 10 shows the relative increment of strontium to calcium in the skeleton divided by the ratio of strontium to calcium in the diet. This ratio is a measure of the overall discrimination for strontium relative to calcium. The derived values are surprisingly close considering the approximations involved in their derivation. That the ratio is less than unity implies an overall discrimination, bone → diet, against strontium. The mean value, 0.17, is less than the value for adults (0.25) derived by Bryant *et al.* (1958). It could be inferred that the overall discrimination between strontium and calcium is rather greater in children than in adults.

Discussion

It is specially noteworthy that 16 days after an oral dose of strontium the mean percentage retained in the skeleton in the case of the children (19.3 ± 2.2) was not significantly different from that for the adults (16.7 ± 2.0)—$0.4 < P < 0.5$. It might be expected that the growth rate in the youthful skeleton would result in a higher uptake of an oral dose of strontium in children compared with adults. For example, in rats it has been shown that the percentage of a single dose of radioactive strontium deposited in the skeleton is about five times greater in young animals than in adults (Copp *et al.*, 1947). It is important to note, however, that the rate of skeletal growth in children of age-group 5–15 years is about 20 times less than in rats about 4 to 5 weeks old.

It is perhaps significant that the mean urinary excretion of calcium for the children was one-third of that for the adults (Table V). This must indicate a relatively lower renal clearance of calcium in the children. That the total urinary excretion of a single dose of strontium was so much less in the case of the children than in the adults (Table VI) suggests that the renal clearance for strontium may also be less in children. However, the present data provide no information on whether there is any difference between children and adults in the renal discrimination between strontium and calcium.

The radiation dose to the skeleton resulting from an ingestion of radioactive strontium cannot be assessed from the present data. Limited experimental evidence obtained in this laboratory (Bishop *et al.*, 1960) on the decrease in the retention of a radioactive dose of strontium in adults shows that it is very rapid during the first 15 days and thereafter becomes progressively slower over the next 200 days. From the form of this retention–time relationship it is shown that this initial period of rapid change in the retention contributes only a small fraction to the total radiation dose to the skeleton from strontium-90 in, say, 200 days. In other words, the integral radiation dose depends principally upon the long-term retention of strontium-90. There is no experimental evidence on the long-term retention following a single dose of strontium to children, and obviously extrapolation beyond the 15-day period covered in the present investigation would be unreliable. However, if the retention–time relationship were to be independent of age, the

TABLE VII.—*Values of the Overall Discrimination* in Children Between Strontium and Calcium Deduced from the Mean Daily Excretion*

Child	Mean Daily Excretion		Mean Skeletal Increment		Calculated Daily Intake		Ratio Skeleton/Diet		Overall Discrimination
(1)	Sr (mg.) (2)	Ca (g.) (3)	Sr (mg.) (4)	Ca (g.) (5)	Sr (mg.) (6)	Ca (g.) (7)	Sr (8)	Ca (9)	Sr/Ca (10)
S.R.W.	0·67	0·54	0·015	0·055	0·69	0·59	0·022	0·093	0·24
M.A.L. ..	1·36	0·86	0·045	0·16	1·41	1·02	0·032	0·16	0·20
A.S.H. (1) ..	3·57	1·51	0·064	0·23	3·62	1·74	0·018	0·13	0·14
,, (2) ..	2·44	1·05	0·064	0·23	2·50	1·28	0·025	0·18	0·14
R.M.	3·28	1·45	0·064	0·23	3·34	1·68	0·019	0·14	0·14

* The overall discrimination between strontium and calcium is taken as the ratio of the daily increase of strontium to calcium in the skeleton divided by the ratio of strontium to calcium in the diet.

integral dose to bone would be from two to four times greater in children than in adults purely as a result of the higher concentration of the radioactive dose in the smaller juvenile skeleton. It is possible that the higher rate of remodelling in the youthful skeleton as compared with the adult would contribute to a higher rate of removal of the radioactive dose in children.

Summary

The daily urinary and faecal excretion of strontium and calcium for four children between the ages of $4\frac{3}{4}$ and $14\frac{1}{2}$ years has been measured over an initial period of seven or eight consecutive days immediately before an oral dose of about 100 mg. of strontium (as strontium chloride) taken at breakfast-time. Subsequently, the daily urine and faecal excretion of strontium and calcium was estimated over a period of from 12 to 18 days and the net retention of the dose deduced. The results are compared with the excretion of an oral dose of strontium by adults from this unit.

The mean, cumulative, urinary excretion of a single oral dose of strontium was about 3% for the children up to 16 days after the dose, with the exception of a boy $14\frac{1}{2}$ years old. The corresponding faecal excretion was about 78% of the dose. The respective excretions, over a similar period, for adults were 19% and 64% of the dose. Thus the retention (dose – excretion) up to 16 days after the dose was not significantly different in the two age-groups.

An attempt made to compare values derived for the overall discrimination of strontium relative to calcium in children and adults tends to show that it is rather higher in children.

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HAEMOPTYSIS

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For most patients and not a few doctors, the expectoration of blood signals either pulmonary tuberculosis or carcinoma. We have been impressed by the number of patients with haemoptysis in whom neither of these conditions was present. A reassessment of this symptom is necessary, particularly since the pattern of respiratory disease has been changing during the past ten years.

Our purposes therefore were: (1) to examine the causes of haemoptysis in chest-clinic practice; (2) to consider whether there are features of the haemoptysis peculiar to different diseases; and (3) to determine the need for follow-up of patients presenting with haemoptysis without apparent cause.

Material and Methods

Haemoptysis is defined here as the expectoration of blood or blood-stained mucus not due to bleeding in the upper respiratory tract or associated with gastro-intestinal bleeding. We recognized that often there was no immediate confirmation of the bleeding, and it was unusual for the patient to be able to produce blood-stained sputum on request. We depended on the patient's account of this bleeding episode, on the observations made by his own general practitioner, and on such further details as we could elicit on close questioning. To facilitate the last, the accompanying form was designed, since we could not hope to find the details required from all patients in any analysis of previous records. A little experience shows that there is

Date of first attendance:

INVESTIGATION OF CASES OF HAEMOPTYSIS

Patient's Name ..... Ref. No. .....

Details concerning the haemoptysis

1. (*a*) Doubtful:
   (*b*) Probable:
   (*c*) Certain:
2. Any associated upper respiratory bleeding:
3. Any history of acute upper respiratory infection:
4. Estimate of the amount of blood expectorated:
5. A frank haemoptysis or merely staining:
6. Single or repeated haemoptysis:
7. Can the patient locate the site of the haemoptysis?
8. Duration of the haemoptysis:
9. Any other bleeding tendency:
10. Smoking history:

Clinical findings

1. U.R.T.
2. B.P.
3. Heart:
4. ? Added sounds in the chest:
5. *X* ray of chest:
6. Predominant pathogens in the sputum:
7. Cultures for *M. tuberculosis*:

Diagnosis

sometimes doubt concerning the origin of the blood. Patients in whom there was either preceding nose- or mouth-bleeding or vomiting were excluded. We separated patients with a history of haemoptysis into the following categories:

Doubtful.—Referred by the general practitioner as "haemoptysis," but the patient was vague about details and was regarded as a poor witness, or further questioning revealed bleeding of the upper respiratory tract about the time of the haemoptysis (but *not* immediately preceding it).

Certain.—Close questioning confirmed the general practitioner's opinion that this was a true haemoptysis. In some cases there was confirmation from the family about the bleeding.

Probable.—Intermediate between the two above.

The remainder of the form is self-explanatory with the following exceptions.—We defined *single* haemoptysis as an episode lasting up to seven days but usually only one to two days, and *repeated* where the bleeding continued longer than seven days or there was a break in continuity of at least two to three days—that is, more than one episode of bleeding. *Frank* haemoptysis denoted the expectoration of pure blood, without sputum.

Routine clinical examination (including blood-pressure) was supplemented by a full-size postero-anterior film of the chest and examination of the sputum (if available) for predominant organisms and *Mycobacterium tuberculosis*. Where there was no sputum and the *x*-ray film was normal, no bacteriological examination was carried out. If the *x*-ray film was abnormal, laryngeal swabs were taken. Sputum cytology was not investigated. While it may be a counsel of perfection to offer bronchoscopy and bronchography to all who complain of haemoptysis, it is doubtful whether this is justified. Bronchoscopy and bronchography were therefore recommended only if the haemoptysis was thought to be certain and was repeated. Where the initial investigations pointed to bronchial carcinoma the patient was referred to the thoracic surgeon. For those in whom the chest *x*-ray film was normal the investigations were completed by ourselves.

Follow-up assessment, which included a further P.A. film of the chest, was arranged three months, six months, one year, and two years after the first attendance. It was essential that our follow-up be as complete as possible, since this had not been achieved in previous reports. When the usual appointment notes failed, a personal letter was written to the patient, and, if this failed, his doctor was approached. If the doctor was unable to help, the health visitor, and then one of us, visited the home and repeated the visits until we were satisfied that these were fruitless.

Results

During 1956 2,187 new patients attended the chest clinic, of whom 324 (15%) gave a history of haemoptysis within the preceding month. The monthly incidence varied from a peak of 30% in February to 8% in July. The February increase was related to a higher proportion of bronchiectasis, pneumonia, and pulmonary tuberculosis.

The patients were predominantly young, with the peak incidence in the third decade (82 patients), but the age distribution covered eight decades (9 were aged 10 years or less and 13 were 70 or more). There were rather more males than females (182/142).

The haemoptyses were classified as follows: doubtful, 48 (15%); probable, 90 (28%); certain 186 (57%).

The total amount of blood expectorated was assessed as follows: Streaking only, 155; more than streaking but less than 5 ml., 95; exceeding 5 ml. but less than 30 ml., 45; exceeding 30 ml., 16; doubtful or not stated at first interview, 13. (Four patients gave a history of large haemoptyses exceeding 300 ml.)

The *x*-ray film of the chest was normal in 168, while in a further 26 the only abnormalities were calcified primary foci (parenchymal scars and/or calcified hilar nodes). We noted that such calcified primary lesions were relatively common. To test the significance of this finding we re-examined the radiographs of all those patients in whom either no abnormality could be found (N.A.D. group) or, at the most, only upper respiratory infection (U.R.I. group)—a total of 145 patients. Twenty-six (18%) showed calcified primary foci (calcified apical lesions were excluded and hilar calcification accepted only if the shadow appeared "craggy" and irregular). A control group was obtained by reviewing the first 200 attendances during the same year in which the diagnosis of N.A.D. or U.R.I. and the age-and-sex distribution approximated, but in which there was no history of haemoptysis. Ten were excluded because re-scrutiny of the *x*-ray film raised doubts whether it was normal. The results of this comparison are shown in Table I. The incidence of calcified primaries was higher in those with haemoptysis, and the observed difference (8.6%) is more than twice the standard error of the difference between the two proportions (3.7%). These calcified primaries have not altered on subsequent radiographs, nor was there any record of a broncholith being expectorated. In those with calcified hilar nodes we have been unable, at bronchoscopy, to see any abnormality of the mucosa overlying the calcified area. Of the 53 patients who had bronchograms, 11 had calcified primary complexes or calcified hilar nodes, but only two had demonstrable bronchiectasis in relation to these areas of calcification.

Sputum studies for predominant organisms in 96 patients revealed no uniform pathogen—a mixture of pneumococci, *Haemophilus influenzae, Streptococcus viridans, Staphylococcus aureus* and *albus*, diphtheroids, and the occasional Friedländer bacillus, and yeasts. On average, two cultures for *M. tuberculosis* were obtained from 173 patients, and in only 14 patients were positive cultures isolated. In no instance were tubercle bacilli discovered without a radiological lesion.

Bronchoscopy was done under local anaesthesia in 51 patients. The straight and right-angle telescopes were used to obtain a systematic view of as many of the segmental orifices as possible. Biopsy was taken only if there was a local lesion. Apart from bronchial carcinoma, the only other abnormalities were the mucosal changes of chronic bronchitis.

Bronchograms were obtained in 53 patients, using aqueous propyliodone. Complete filling of all the

TABLE I.—*Relation Between Haemoptysis and X-ray Evidence of Calcification*

	No. of Patients	Calcified Scars or Calcified Hilar Nodes
Haemoptysis (N.A.D. + U.R.I.) ..	145	26 (18%)
Control ,, ,, ,, ..	190	18 (9%)

Observed difference, 8·6%; S.E. 3·7%.

segmental branches in both lungs was achieved except in the elderly with limited respiratory function.

Diagnosis

The final diagnoses are listed in Table II. As some patients had more than one diagnosis the total in this table exceeds 324.

TABLE II.—*Diagnoses in 324 Patients with Haemoptysis*

Upper respiratory infection		77
N.A.D.		68
Bronchitis		56
Bronchiectasis		43
Pulmonary tuberculosis	Active	14
	Quiescent	18
Pneumonia		20
Cardiovascular disease	Essential hypertension (diastolic >100 mm.)	16
	Mitral valvular disease	7
Carcinoma		14
Others		4

The pneumonias were all of less than lobar extent and usually segmental as judged by the radiographs. Bronchitis, with the exception of three acute forms, was chronic—defined here as a history of productive cough over at least two years and associated with some disability, either dyspnoea or a record of time lost from work owing to "bronchitis." The diagnosis of bronchiectasis was confirmed in less than half the cases because we reserved bronchoscopy and bronchograms for patients with repeated haemoptysis, and bronchography for those in whom we considered confirmation of the diagnosis would determine the line of treatment. Of the cases of active pulmonary tuberculosis seven were minimal and seven moderately advanced. *M. tuberculosis* was recovered from all these patients.

The low incidence of carcinoma and active pulmonary tuberculosis in this series as cause of haemoptysis (each only 4%) is notable. No bronchial adenoma was discovered. Cardiovascular disease was infrequent, but was an expected finding, as patients with known cardiac disease were generally referred to the cardiac clinic or the out-patient department of a general hospital. No pulmonary infarct was found.

Only 16 patients had systemic hypertension, defined here as a diastolic reading exceeding 100 mm. Hg. The incidence in the group as a whole is therefore low (5%). There was no recurrence of the haemoptysis in these patients despite a rising diastolic pressure in two (140 mm. in one and 160 mm. in the other); further, no other bleeding tendency was detected.

Character of Haemoptyses in Relation to the Cause

We have analysed the type, duration, and sequence of bleeding and can recognize minor differences in bronchial carcinoma, active pulmonary tuberculosis, and bronchiectasis (Table III). The haemoptysis of active tuberculosis and bronchiectasis tended to be brisk and of short duration, while that of carcinoma was more prolonged. In 3 of the 14 carcinoma cases the haemoptysis was *not* defined as "certain." In chronic bronchitis there was no distinctive pattern; usually the haemoptysis was "certain," a single episode with only streaking of the sputum. A frank haemoptysis was uncommon (only 10 patients).

TABLE III.—*Haemoptysis Pattern*

	Carcinoma (14 Patients)	A.P.T. (14 Patients)	Bronchiectasis (17 Patients)
"Certain"	11	13	15
"Streaking"	10	3	10
"Frank"	2	8	8
"Repeated"	9	7	11
Duration	10=2 weeks or longer	10=1 week or less	12=3 days or less

Follow-up

Over a two-year period 20 patients died, 14 from cancer of the lung and 6 from cardiovascular disease. Only one of these died during a further haemoptysis. Of the remaining 304 patients, 279 (91.8%) have been examined one year and 273 (89.8%) two years after their first attendance. Of the 31 who were not examined at the end of two years, 10 have been interviewed and appear well and are working but have refused further *x*-ray examination. Of the remaining 21, 16 have left the city, four cannot be traced, while one elderly lady is confined to bed at home with "bronchitis." In 18 of the 273 patients the final *x*-ray film of the chest at two years was not a full-size P.A. film but a 35-mm. M.M.R. film taken during the 1958 M.M.R. campaign. We have re-scrutinized these M.M.R. films and are satisfied that they are normal.

At the final review several patients denied the history of blood expectoration given at their first visit; consciously or unconsciously, they contradicted their original history. This amnesia underlines the need for careful recording at the first visit and is a reminder of the limitations of the retrospective survey.

In the course of the follow-up the diagnosis was eventually confirmed in one and corrected in three other patients.

A man aged 47 with a history of certain and repeated haemoptysis and a suspicious left hilar shadow. He refused investigation but 11 months later agreed, and was found to have a squamous carcinoma of bronchus which was inoperable.

A man aged 67 whose initial assessment was "chronic bronchitis." Bronchogram showed a segmental filling defect, considered at the time to be due to inadequate filling. Reinvestigation three months later because of a recurrence of his haemoptysis revealed a squamous carcinoma of the bronchus, for which left pneumonectomy was performed.

A man aged 39 was initially assessed as "minimal observation pulmonary tubercle" and kept under review. Three months after haemoptysis this lesion cavitated, with a minimal spread and sputum positive for *M. tuberculosis*.

A woman aged 20 was a contact of known pulmonary tuberculosis. *X*-ray film at time of haemoptysis was considered normal, an opinion confirmed on re-scrutiny. She was kept under review, and 10 months later developed a minimal focus in the right upper zone, with sputum positive for *M. tuberculosis*.

Discussion

Chronic bronchitis is certainly an important cause of haemoptysis, and, in view of the bronchoscopic appearances in this disease, blood-staining of the sputum is not surprising. Smidt (1957) has described "sites of predilection" for haemoptyses—the areas around the orifices of the upper-lobe bronchi. These areas, however, can usually be examined more systematically than the lower bronchi. Though small bleeding-points were often noted in our bronchitic patients, we observed no special localization, but in some of the patients slight pressure from the top of the bronchoscope caused a small bleeding-point. It is probable that acute paroxysms of coughing can cause bleeding of the congested and inflamed mucosa of the bronchitic. We believe that this is an important cause of haemoptysis at the present time.

Of the 177 new notifications of active pulmonary tuberculosis in 1956, only 14 (8%) presented with haemoptysis, a lower proportion than reported by any

previous authors. In part, this is due to an increasing proportion of minimal lesions and fewer with moderately or far-advanced disease, but half of our patients were already moderately advanced. Comparison of the pattern of haemoptysis showed curiously larger amounts of blood recorded by those with minimal disease (six out of seven patients had noted 5 ml. or more of blood, compared with three out of seven with moderately advanced disease). But those with cavitary disease recorded a *repeated* haemoptysis in six out of seven, compared with only three out of seven with minimal disease. Apart from these differences, we could determine no other feature peculiar to haemoptysis in active pulmonary tuberculosis. Only one of these patients presented with a normal *x*-ray picture. She was a young woman aged 20 who was already attending the contact clinic. Her minimal lesion came to light 10 months after her haemoptysis and would, in any case, have been discovered.

Among those with quiescent pulmonary tuberculosis the haemoptysis was usually a single episode with only streaking of the sputum. In none of these patients was there any late reactivation of their tuberculous foci and, indeed, the haemoptysis was probably coincidental.

The character and degree of bleeding among our patients with bronchiectasis approximated to the pattern, for patients with active pulmonary tuberculosis. There was no difference between patients with cylindrical (8) or saccular (9) bronchiectasis.

In bronchial carcinoma the notable feature of the haemoptysis was its *duration*, which in the majority was at least two weeks. During this same year we saw 26 new patients with bronchial carcinoma, of whom 14 had haemoptysis. In 13 of these 14 patients a tumour was seen at bronchoscopy, and in 11 there was histological proof (seven squamous cell, one adenocarcinoma, and three anaplastic). These numbers were too small to recognize differences in the history of haemoptysis.

The problem of the patient with haemoptysis and a normal *x*-ray picture of the chest has been discussed by Mitchell (1955), who, among 30 such patients, found four with proved carcinoma and another two probable. Somner *et al.* (1958) report 93 patients, five of whom had bronchogenic carcinoma, and they note that these tumours all came from the 55 patients over the age of 40. Including 26 with calcified primary foci, 194 of our patients had a normal *x*-ray picture of the chest and only three of these were found to have a bronchial carcinoma (two proved, and one probable in an elderly patient who died at home). These three patients were men over the age of 40. The likelihood of carcinoma in a man over the age of 40 with an *x*-ray picture of the chest which shows nothing abnormal is therefore probably no higher than one in eight. We agree, however, with Somner *et al.* (1958) that bronchoscopy is advisable in men over 40 with a record of haemoptysis, even though their chest radiographs are normal.

At the start of this survey we felt that some follow-up of patients with haemoptysis was necessary, but it was a matter of conjecture how long this should be. We believed then that a year was necessary and two years desirable. The evidence we have accumulated from this series of patients shows that follow-up is not necessary.

Conclusions

Among 324 patients with haemoptysis we have been unable to find a cause in 145 (44%). Inflammatory conditions of the bronchi, chronic bronchitis, and bronchiectasis accounted for 30% of the total and were more than seven times as frequent as either bronchial carcinoma or active pulmonary tuberculosis. Calcified primary complexes may render patients more prone to haemoptysis, though the mechanism is in doubt and we have no proof of a causal relation. Systemic hypertension is an uncommon cause of haemoptysis.

In carcinoma, haemoptysis tends to be minimal but persistent; a frank haemoptysis is unusual and the certainty of the haemoptysis may be in doubt. It is still an important and frequent symptom in this disease.

In active pulmonary tuberculosis there is a brisker bleeding of short duration and the incidence of this symptom has declined.

We confirm that the amount of bleeding is no index of the underlying pathology.

Over a two-year period 89.8% of these patients were followed up. So little change was shown that we believe that follow-up is not necessary, provided the patients are carefully assessed at the first examination. In men over the age of 40, in whom the risk of carcinoma is higher, bronchoscopy is an essential part of the initial investigation.

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CLINICAL EVALUATION OF PROMAZINE AS AN ADJUNCT TO PREDELIVERY SEDATION

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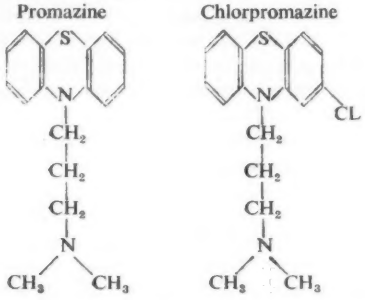
In recent years little progress has been made in obstetric practice with regard to analgesia and sedation in labour. The principal drugs used universally are still the barbiturates, pethidine hydrochloride, morphine and its derivatives, and scopolamine. None of these, however, satisfies the requirements of the ideal analgesic in obstetric practice. With the advent of the tranquillizing drugs, it was hoped that a new agent might be found which would provide satisfactory neuromuscular relaxation with relief of pain and tension in labour without untoward side-effects on either the mother or child.

Attention was directed to the phenothiazone series because of the potentiating effect of the various compounds in this group on hypnotics and analgesics. The effect of chlorpromazine as a sedative in labour has been reported by several authors (Karp *et al.*, 1955; Anz and Smith, 1956; Schaffer, 1956; Norton *et al.*,

1956). The results, however, have been disappointing and unreliable, and the risk of a precipitate fall in the blood-pressure when the drug is administered intravenously has proved an alarming side-effect.

A related compound, promazine ("sparine"), has a similar chemical structure to chlorpromazine, but lacks the chlorine atom. The difference in chemical structure is shown in the formulae.



Promazine has a depressive action on the subcortical centres of the central nervous system, reducing the intensity of abnormal stimuli without producing undue sedation or alteration in autonomic function. This blocking of afferent stimuli lessens emotional tension and decreases the awareness of pain, which should be of value during labour (Carlo, 1957; Himwich, 1958).

Toxic Effects

Few toxic effects of the drug have been published. Woodward and Solomon (1956) first reported a fatal case of agranulocytosis on the forty-eighth day of promazine therapy in a psychiatric patient. Several other cases have been published since (Cook *et al.*, 1957; Earle, 1957; Glaser and Adams, 1958). In a report to the A.M.A. Council on Drugs (1957) 18 cases of blood dyscrasia associated with promazine hydrochloride were listed, four of which ended fatally. In each of these reports the drug had been given for a prolonged period in the treatment of psychiatric conditions. Moore (1957) discussed the development of local reaction at injection sites, due probably to leakage into subcutaneous tissue. Opinsky *et al.* (1958) reported a case, which was later commented on by Root (1959) and Hamelberg (1959), in which arterial spasm and peripheral gangrene followed the presumed intra-arterial injection of promazine hydrochloride.

Buckmaster (1957) described a case of overdosage of promazine in a barbiturate addict who had taken 2,200 mg. of the drug. Though there was a considerable fall in blood-pressure, no respiratory depression or anoxia occurred.

Promazine hydrochloride would therefore seem to be a less dangerously toxic drug than chlorpromazine hydrochloride.

Previous Work Carried Out

Numerous publications have appeared describing the use of promazine in psychiatric disorders, but there have been only four reports on its use in labour. Sprague (1957) reported a series of 677 unselected cases in which promazine was administered during active labour. After an initial trial in 27 cases, 650 patients were given promazine hydrochloride, 50 mg., combined with pethidine hydrochloride, 50 mg., and scopolamine, 1/100 gr. (0.65 mg.), by intravenous injection when labour was established. He claimed excellent analgesia in 86% of cases and a good result in a further 13%. Labour was generally shorter and no foetal respiratory depression was observed. Side-effects were claimed to be minimal, two cases developing a mild hypotension and one a thrombophlebitis at the site of injection.

Kuntze and Sison (1957) studied the effect of promazine hydrochloride in 100 unselected cases, 50 mg. being administered intravenously to all patients in established labour. All but 16 required pethidine or atropine in addition. 70% had excellent relaxation and 25% a good result. No side-effects were noted.

Wegryn and Marks (1958) discussed the value of promazine and pethidine in association with spinal anaesthesia for labour and delivery in 100 unselected cases. All patients were given promazine hydrochloride, 50 mg. intravenously, when labour was established, followed by the intravenous injection of pethidine hydrochloride, 50 mg., as and when necessary. An excellent result was obtained in 57% of cases, a good result in 29%, and 31% had amnesia of some degree. No adverse side-effects were noted.

Sippel (1958) reported the use of promazine intramuscularly in 100 patients in labour and claimed results as satisfactory as with intravenous administration.

In none of these trials was a control series observed simultaneously, and it was evident that this would have to be done before a correct evaluation of the drug in labour could be made.

Clinical Procedure

Unselected cases admitted in labour were allocated to one of four groups consecutively, so far as their initial sedation was concerned.

Group 1. Promazine hydrochloride, 50 mg., and pethidine hydrochloride, 50 mg., combined and given intravenously.

Group 2. Promazine hydrochloride, 50 mg. intravenously alone.

Group 3. Pethidine hydrochloride, 50 mg. intravenously alone.

Group 4. Any other sedation, but consisting usually of an initial dose of pethidine hydrochloride, 100 mg. intramuscularly.

After the initial drug was injected, further sedation was given as required, in the majority of cases pethidine hydrochloride being injected intramuscularly. The patients were all nursed under the same conditions, and gas and air and "trilene" analgesia were available in the second stage of labour. Most of the patients were confined to bed during labour.

In all, 400 cases were investigated, 50 primigravid and 50 multigravid patients being studied in each group.

Sedative and Amnesic Effects

The response of the patients with regard to sedative and/or amnesic effects was graded as (1) good, (2) fair, and (3) little or no benefit. Subjective impressions were assessed by interview with the patients at various times after delivery. Of the patients receiving the combination of pethidine and promazine, 60% had a good result, as did 52% who had the promazine alone.

These patients became quiet and relaxed within four to five minutes of the injection and some slept soundly, even during contractions. Others were roused by the pains. In groups 1 and 2 20% had varying degrees of amnesia.

A fair sedative result was obtained in 26% and 28% respectively in groups 1 and 2. Few of these had any amnesia. Little or no benefit was found in 14% of group 1 as compared with 20% in group 2.

It was noted that those who had only a fair result, or who had no benefit, had received the initial sedation relatively later in labour, in each instance the cervical dilatation having been estimated at four fingerbreadths or over at the time of injection. If given at this stage the nursing staff occasionally found the patients less co-operative in the second stage of labour.

In groups 3 and 4, which were taken as controls, 42% had good effect, 26% fair, and 32% little or no benefit. No amnesia was found.

In Table I these findings are compared with those of Kuntze and Sison.

TABLE I.—*Comparison of Sedative Effect*

Effect of Sedation	Group I	Group 2	Groups 3 and 4	Kuntze and Sison's Figures
Good	60%	52%	42%	70%
Fair	26%	28%	26%	25%
Little or no benefit	14%	20%	32%	5%

Promazine hydrochloride would appear to be as effective as a sedative, especially if given early in labour, as other drugs in common use.

Effect on Length of Labour

The average length of labour in primiparae and multiparae in each group is shown in Table II. It should be stated that the term "multiparae" includes patients who may not previously have had a full-term pregnancy but had been gravid before. Cases in which labour was terminated by caesarean section are excluded. There is surprisingly little difference among the four groups. These patients who received intravenous pethidine alone seem to have had, on average, a slightly shorter labour. The interval between the initial injection and delivery was also calculated

TABLE II.—*Average Duration of Labour*

	Group 1	Group 2	Group 3	Group 4
Primiparae ..	20 h. 8 m.	19 h. 30 m.	18 h. 25 m.	22 h. 51 m.
Multiparae ..	14 h. 5 m.	14 h. 20 m.	12 h. 52 m.	13 h. 13 m.

TABLE III.—*Initial Injection to Delivery Interval*

	Group 1	Group 2	Group 3	Group 4
Primiparae ..	9 h. 29 m.	9 h. 14 m.	6 h. 6 m.	13 h. 13 m.
Multiparae ..	3 h. 30 m.	6 h. 18 m.	3 h. 24 m.	4 h. 14 m.

(Table III). As would be expected, a fairly consistent figure is present in each group. At least it can be said that promazine has not an adverse effect on the length of labour.

Effect on Amount of Analgesic Used in Labour

A surprisingly high number of patients, both primiparous and multiparous, had only the initial amount of sedation during the whole of labour (Table IV). The initial high dose of pethidine hydrochloride given in group 4 accounts for the high figure in the multiparous patients in this group. There is a corresponding lower figure for the primigravid patients in this group. It is interesting to note also that the figures for promazine and pethidine and for

TABLE IV.—*Number of Patients in Whom Initial Dosage was Sufficient (50 Primiparae and 50 Multiparae in Each Group)*

	Group 1	Group 2	Group 3	Group 4
Primiparae ..	29	24	29	20
Multiparae ..	41	31	31	42

TABLE V.—*Total Amount of Sedation as Averaged Per Patient, Expressed in mg. of Pethidine Hydrochloride*

	Group 1	Group 2	Group 3	Group 4
Primiparae ..	79	74	86	136
Multiparae ..	72	40	79	129

pethidine alone given intravenously are similar in primigravid patients. In the multiparous patient, however, the combined dose seemed to be sufficient for the whole of labour on more occasions.

The actual total amount of pethidine hydrochloride given per patient was also calculated (Table V). This calculation excluded patients delivered by caesarean section and two or three patients in each group who had been given morphine or other drug in labour. There would appear to be little difference among the first three groups, apart from the fact that the giving of promazine would seem to reduce the amount of pethidine required. It is very striking, however, how much more efficient intravenous therapy is than intramuscular therapy, using the same drug. The total amount of pethidine used is much reduced when given intravenously.

Effect on Mode of Delivery

The mode of delivery is shown in Table VI. The patients were not separated into primiparous and

TABLE VI.—*Mode of Delivery in Each Group*

	Group 1	Group 2	Group 3	Group 4
Spontaneous vaginal delivery	80	82	81	79
Forceps delivery	16	16	14	17
Caesarean section	4	2	5	4

multiparous. Promazine would appear to have no adverse effect on the outcome of labour and the spontaneous vaginal delivery rate is not lowered.

Effect on the Third Stage of Labour and the Perineum

To ensure that there was no harmful effect on the third stage of labour with regard to post-partum haemorrhage or retained placenta, the percentage rate of these conditions was compared in groups 1 and 2 (those receiving promazine) with groups 3 and 4 as controls (Table VII). Similarly, the percentage rate for episiotomy and perineal tears was

TABLE VII.—*Percentage of Post-partum Haemorrhage and Manual Removal of Placenta After Promazine and in Controls*

	Promazine Groups	Control Groups
Post-partum haemorrhage ..	3·5%	3%
Manual removal	3%	4%

calculated (all cases of caesarean section were naturally excluded) and corrected to the first decimal figure: promazine groups, 50.8%; control groups, 50.8%.

Effect on Actual Uterine Action

External tocographic records were made before and after injection in six cases receiving promazine alone or combined with pethidine hydrochloride. In no case was there any indication of alteration of uterine muscle activity.

Effect on the Foetus

In the two groups who had received promazine there were five still-births out of 199 cases in which the foetus was still alive at the onset of labour. Two of these, however, had gross degrees of foetal abnormality. In the control groups there were three stillbirths out of 198 similar cases. One of these had a gross degree of foetal abnormality. None of the stillbirths could be attributed to the sedation given. In three cases of the whole series there was evidence of intrauterine death before the onset of labour.

In all other cases the condition of the foetus at delivery was classified as (1) active, where the child cried within two minutes of birth, and (2) lethargic, where active resuscitative measures were required.

In Table VIII the total number of lethargic babies in the series is reviewed.

TABLE VIII.—*Incidence of Lethargic Babies in Each Group*

Group	Total Lethargic	Lethargic after Spontaneous Vaginal Delivery	Lethargic after Forceps Delivery		Lethargic after Caesarean Section
			Local	General	
1	19	10	1	7	1
2	16	8	1	7	0
3	15	6	1	4	4
4	25	10	2	11	2

There was a relatively higher number of lethargic babies after forceps delivery under general anaesthesia, irrespective of the nature of the previous medication. Table IX shows the relationship in this respect between

TABLE IX.—*Condition of Baby After Forceps Delivery by Local and General Anaesthesia. All Groups. Excludes Two Cases of Intrauterine Death and One Stillbirth*

Baby	General	Local
Active	26%	76%
Lethargic	74%	24%

those delivered by forceps under pudendal-block local anaesthesia and those under general anaesthesia. Where operative delivery is concerned it would seem that the condition of the child is more often attributable to the anaesthetic than to the predelivery sedation.

It can be concluded that the use of promazine has no effect on the foetal respiratory centre, even when given shortly before delivery, since in the series some cases received the injection within two hours of delivery.

Side-effects

With regard to the mothers, no patient had an untoward reaction to the intravenous injection of promazine, such as fall in blood-pressure, sensitivity, reaction, or pain at the site of injection. As stated previously, these patients were mainly confined to bed.

One interesting feature observed in those cases in which promazine was administered was a rise in the foetal heart rate occurring within one to two hours after the injection and often, though not invariably, accompanied by an increase in the maternal pulse rate. The foetal heart rate in about 15% of cases rose to between 160 and 180 beats a minute, and was maintained for several hours at this rate. There was no other evidence of foetal distress. In no case did this phenomenon seem to influence the condition of the child at birth. No satisfactory explanation for this has been found.

Summary and Conclusions

A clinical evaluation of the obstetrical use of a tranquillizing drug, promazine hydrochloride, is described and its safety established. A brief review of the previous literature concerning tranquillizers in labour is given.

Promazine hydrochloride, when used in labour, would seem to have no adverse effect on the course of labour and, by its use either alone or in combination with pethidine hydrochloride, will cause a degree of amnesia in some cases and adequate sedation in most. Its use also will tend to lower the total amount of analgesic and sedative required, which may benefit both the mother and foetus. The phenomenon of rise in the foetal heart rate does not seem to affect the foetus, but requires further consideration. The findings in this clinical trial have been contrary to previous work, in that the high frequency of successful sedation, and shortening of labour, have not been confirmed. Promazine, however, would seem to have a definite place in the nervous primigravid early in labour.

It is readily appreciated also that pethidine hydrochloride given intravenously is as efficient in smaller dosage (such as 50 mg.) as when a larger dose (such as 100 mg.) is given by intramuscular injection.

We thank Professor Ian Donald for initially stimulating interest in promazine and Dr. D. McKay Hart for allowing his patients to be subjected to the trial. We also thank Dr. B. W. Cromie, of John Wyeth and Brothers Ltd., for his helpful advice and criticism.

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FAMILIAL RECURRENT OROGENITAL ULCERATION

BY

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Recurrent aphthous ulceration of the mouth is common, its aetiology is unknown, and treatment is unsatisfactory. A small proportion of persons with this complaint also suffer recurrent ulceration of the genitalia. A still smaller fraction of these persons develop serious ocular complications at some stage in the illness. Recurrent oral and genital ulceration together with hypopyon iritis constitute the "triple symptom complex" of Behcet. Several authors accept two of the three manifestations as criteria for the diagnosis of Behcet's syndrome (Berlin, 1944; Phillips and Scott, 1955; Curth, 1956; Wadia and Williams, 1957).

Since the aetiology of these syndromes of muco-cutaneous ulceration is unknown their relationship to one another is also not known. Further data are required; therefore it is thought worth while to record a family in which recurrent oral and genital ulceration affects two siblings, while in a third there is oral ulceration accompanied by ocular inflammation. One of these three siblings also has discoid lupus erythematosus. All three patients also have recurrent herpes of the lips, and viral studies were carried out on the two from whom serum was available.

The first patient was seen in July, 1958, with a complaint of recurrent ulcers of the mouth and of genital ulceration. Her sister is similarly affected. A brother who also suffers from mouth ulceration and recurrent conjunctivitis has been examined, and further data have been collected from his family doctor, a consultant dermatologist, and an ophthalmologist. Information about the sister has been obtained from her local practitioner and three dermatologists, and from her answers to written questions. These three members of the family have been living considerable distances apart for the past five years.

There are five brothers and two sisters in the family. A sixth brother died from renal failure of unknown cause at the age of 24. The mother has had corneal ulceration on two occasions, but old notes of her case cannot be found. The other members of the family are well.

Case 1

A 24-year-old nurse first suffered from mouth ulcers when she was 13 years old. These start as small white lumps which become red, blister, then ulcerate, and they occur on the tongue, buccal mucosa, and pharynx. They last from 7 to 10 days. Since that time these ulcers have occurred with great frequency in crops. There have been intervals of freedom of several weeks, but in the past year she has never been quite free of them.

At the age of 14 ulcers first occurred on the external genitalia. They came in crops of as many as four, as large as 1 cm. in diameter, occurred about six times in a year, and were mainly on the inner surfaces of the labia minora. She has been free of these since the age of 17. From that time until she was 22 she had red painful eyes with some photophobia several times a year. There was no sticky exudate, however. There seemed to be no relation in time between mouth ulcers and the red eyes. She quite often has herpes of the lips, but this does not usually coincide with mouth ulceration. There have been no rashes, symptoms of nervous system or urinary tract involvement, or thrombophlebitis. She has chilblains in cold winters, and often has Raynaud's phenomenon.

An acute exacerbation was observed closely in January, 1959. This began with a vague feeling of tiredness and ill-health for two days, after which several white nodules appeared in the mouth, which became red, then vesicular, and ulcerated after 24 to 36 hours. On this occasion a herpes simplex eruption 1.5 cm. in diameter developed on the right side of the lower lip simultaneously with the mouth ulcers. She had a dull right-sided frontal headache for two to three days, and had felt a little feverish.

On examination the patient was afebrile. There were three quite deep ulcers in the mouth, on the right anterior faucial pillar and on the buccal surfaces of the right upper and lower jaws, each being approximately 1 cm. in diameter with sharp edges and a white sloughy base 1–2 mm. below the surface. Two lymph nodes below the right side of the mandible were considerably enlarged and tender. The eyes were quite normal. Examination with the slit-lamp microscope showed no evidence of inflammation. There was no ulceration or scarring of the external genitalia. Ward testing and microscopical examination of the urine were negative.

Laboratory Investigations.—Blood count: Hb, 13.8 g./100 ml.; normal red cells; W.B.C., 9,100/c.mm. (polymorphs 85%, lymphocytes 3%, monocytes 10%, eosinophils 2%). Serum electrophoretic pattern: total protein, 8.78 g./100 ml. (albumin 4.88 g., α_1-globulin 0.30 g., α_2-globulin 0.62 g., β-globulin 0.88 g., γ-globulin 2.10 g.). L.E. cell tests were negative on two occasions. Erythrocyte sedimentation rate (Westergren): 97 mm. first hour. Viral studies: no viruses were isolated in newborn mice from swabs of the ulcer.

Herpes Neutralization Test.—A modification of the method of Scott (1956) was used. Details of the test are briefly: (1) Sera inactivated for 30 minutes at 56° C., and fourfold serial dilutions prepared. (2) Equal parts of virus suspension (herpes "Craig" strain, mouse-brain suspension passage 5—a local strain), approximately 100 LD_{50} added to serum, and mixtures left at 4° C. for one hour. (3) 0.03 ml. of mixture inoculated intracerebrally into groups of five 3- to 4-weeks-old mice under ether anaesthesia. (4) Deaths recorded daily for 14 days. (5) Neutralizing indices determined, using the method of Reed and Muench (1938).

Results.—Serum taken on January 17, 1959, during the exacerbation of mouth ulceration yielded a neutralizing index of $10^{-2.81}$, whereas serum on February 11 gave an index of $10^{-2.65}$. This rise in titre is not significant.

Treatment.—Local hydrocortisone and triamcinolone have been used. The patient dissolves these in her mouth as close as possible to the sore areas. She did not have relief with hydrocortisone tablets (2.5 mg.), but felt that triamcinolone tablets, 1 mg. four times a day, helped the discomfort during the severe attack in January. There was no rapid improvement, and the ulcers healed over a period of 10 days. Subsequently, however, she has been convinced that early use of the tablets has stopped the development of ulcers.

Six weeks after the January exacerbation there was no residual scarring in the mouth. The E.S.R. was 67 mm. in the first hour (Westergren). She felt well apart from slight soreness of the mouth due to three small shallow ulcers.

Case 2

The 22-year-old brother of the above patient, a farmer, has suffered from recurrent stomatitis for eight years and from conjunctivitis for six. The oral ulcers come in crops of three or four and last for 7 to 10 days. Some fruits, such as pineapple, and tiredness are thought to be precipitating factors. He has had "cold sores" on several

occasions, but he does not remember them coinciding with crops of mouth ulcers. Mouth ulcers occur at intervals of a week to two months, and conjunctivitis occurs with similar frequency. He also suffers from severe cystic acne of the chest and face. He has never had any ulceration of the genitalia.

In November, 1957, he was seen by an ophthalmologist, who diagnosed conjunctivitis; this responded satisfactorily to treatment with an antibiotic ointment. He was seen again in December, 1958, with a painful red right eye, and was found to have an active marginal keratitis. Slit-lamp examination revealed no inflammatory signs in the anterior segment of either eye. The ulcers were carbolized, and he was treated with hyoscine and hydrocortisone drops. Further cauterization was required two days later, after which the inflammation subsided. The only feature of note on examination in March, 1959, was a little scarring of the buccal mucosa on the anterior pillars of the fauces. The blood count was normal. The E.S.R. in this quiescent phase was 24 mm. in the first hour (Westergren). The serum protein electrophoretic pattern was: total protein, 8.84 g./100 ml. (albumin 4.85 g., α_1-globulin 0.22 g., α_2-globulin 0.96 g., β-globulin 1.06 g., γ-globulin 1.75 g.). Herpes neutralization test gave a neutralizing index of $10^{-3.35}$.

It is of interest that this man's fiancée, aged 20, whom he has known for several years, has had mouth ulcers during the last two years. She usually has no more than three small ulcers not greater than 3 mm. in diameter at any time, and they last only three days. They are brought on by tiredness. She did not have these ulcers before she met her fiancé.

Case 3

The 29-year-old sister of the above patients, married with two children, has suffered from ulcers in the mouth since early childhood. She has a dozen or more at once, up to 5 mm. in diameter, occurring, at present, approximately every two months, though attacks used to be much more frequent. They last from 7 to 10 days. She also had genital ulcers of about the same size and duration, starting at the age of 15, and occurring every few weeks. These were most frequent in her 16th and 17th years, but they still trouble her occasionally when there is very bad mouth ulceration. The last crop occurred 18 months ago. Apart from one isolated attack of conjunctivitis, there has been no ocular disease.

Oral ulceration is precipitated by nervous stress and worry or tiredness. There is, in addition, an extraordinary association of lupus erythematosus in this woman. Three consultant dermatologists have agreed that the purplish-red scaly lesions on each cheek precipitated by sunlight represent discoid lupus erythematosus. Like her sister, she has chilblains and very persistent Raynaud's phenomenon in the winter.

Her 3-year-old daughter has recently had a crop of small ulcers in the mouth, without any other manifestations of Behcet's syndrome.

Discussion

In the present state of knowledge it is impossible to say whether these cases are incomplete examples of Behcet's syndrome or whether they are examples of a more benign type of recurrent aphthosis. It may be significant that in Cases 1 and 2 there is a history of minor ocular inflammation.

There are a number of recorded cases in which recurrent oral and genital ulceration preceded iritis by many years—for example, 21 years in Whitwell's Case 1 (1934). Franceschetti, Valerio, and Babel (1946) have emphasized that fully developed iritis is often preceded by attacks of photophobia and redness, sometimes by a considerable time.

It is uncertain whether the cases recorded here are incomplete forms of Behcet's syndrome, and whether, therefore, it would be desirable to attempt to forestall the development of iritis. Unfortunately it is not known if adrenal corticosteroids would do this, and, in any case, the dangers of long-term cortisone therapy may not be justified to prevent this complication without more certain knowledge of its rate of occurrence.

Steroids have favourably influenced several cases (Phillips and Scott, 1955; Linton and Saint, 1956). In our Case 1, small doses of triamcinolone dissolved locally have in the opinion of the patient helped to prevent severe ulcers from developing, and have relieved the discomfort, but they have not reduced the time taken for lesions to heal.

Sircus, Church, and Kelleher (1957) have shown that a family history is common in aphthous stomatitis (45.8% in their series), but they do not mention the familial incidence of combined oral and genital ulceration. Doubtless this is much more common than is realized. Of their 120 patients, 80 were women. Twelve (15%) of these had periodic involvement of the vulva or vagina; whereas the genitalia were involved in only two (5%) male patients. The triple syndrome of Behcet does not appear to have been observed as a familial disorder.

The aetiology of recurrent aphthous ulceration, recurrent orogenital ulceration, Behcet's syndrome, and the other synonymous syndromes is unknown. The data quoted by Sircus *et al.* (1957) on the results of the complement-fixation test for herpes virus in aphthous stomatitis showed a greater incidence of positive reactions in cases with a history of herpes. While recurrent aphthous ulceration and herpes often coexist, the evidence seems to be in favour of their being separate conditions; but it could be construed in a different way: some cases of recurrent aphthous ulceration could be due to herpes, and some could be due to infection by different viruses. The results of our virus studies showed the presence of herpes antibodies in the two patients from whom sera were obtained, though viruses were not grown from the ulcers of Case 1. The titre of herpes antibody in this patient did not rise significantly during the attack.

The finding of discoid lupus erythematosus in one patient is interesting. In the other two cases the high erythrocyte sedimentation rates and possibly the raised gamma-globulin levels of the blood could be reflections of an underlying systemic disturbance. Mouth ulceration has been noted as a feature of systemic lupus erythematosus (Harvey *et al.*, 1954). It is very tempting to speculate on whether the finding of discoid lupus erythematosus may be more than fortuitous.

More data are needed to define the associations between recurrent aphthous ulceration, recurrent orogenital ulceration, and Behcet's syndrome.

Summary

The unusual situation of two sisters suffering from long-standing recurrent oral and genital ulceration and of a brother with recurrent buccal ulceration and conjunctivitis is described. Recurrent herpes labialis occurs in each case. Viral studies were carried out on two of these patients. The herpes neutralization test showed a significant titre of antibodies to the virus of herpes simplex in two patients, though no virus could be grown from the ulcers in Case 1, from which culture was attempted.

These are possibly incomplete forms of Behcet's syndrome, but it is not known at present how many cases of recurrent orogenital ulceration ultimately develop iritis, the third symptom of Behcet's triad.

Laboratory tests in two patients showed evidence of a systemic disturbance, while the third was found to have discoid lupus erythematosus.

The herpes neutralization tests were carried out by Mr. Brian Moore, of the Institute of Medical and Veterinary Science, Adelaide.

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BACTERAEMIA IN HUMAN BRUCELLOSIS

BY

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The studies presented in this paper were undertaken to investigate the incidence of bacteraemia in human brucellosis at Malta, and to find out the relationships between recovery of brucella from blood and from marrow as well as between bacteraemia and pyrexia.

Methods and Results

A study was carried out on the result of blood cultures drawn from 93 cases of brucellosis that were admitted to medical wards of St. Luke's Hospital, Malta, without having yet received antibiotic treatment. In one of these cases (Case 1) blood was drawn and cultured three times. In 11 cases blood was drawn and cultured twice, first for diagnostic purposes, and then to correlate the results of cultures of blood and marrow drawn simultaneously as described below. In no instance was antibiotic treatment started before these samples had been collected. The total number of blood cultures was 106. At least 5 ml. of blood was collected by sterile syringe from an antecubital vein and cultivated in tryptose broth and agar, using Castaneda's combined method of culture. No sample was stated to be sterile until 21 days had elapsed. Where culture was negative the diagnosis was based on serum agglutination of *Brucella melitensis* at a titre of at least 1 in 160 at some period of the disease. *Br. melitensis* was recovered from 69.8% of instances (Table I).

The results of 45 bone-marrow cultures drawn from the sternum of 45 out of the 93 patients were also studied. The samples were obtained by aspirating at least 2 ml. of bone-marrow into sterile syringes fitted with Salah needles, and were cultivated by the same method as described for blood. The presence of marrow in the drawn samples was confirmed in all instances by demonstrating marrow cells in slides that were prepared from samples. *Br. melitensis* was recovered from 66.7% of samples (Table II). When the results of cultures of blood and of marrow samples, collected simultaneously from 35 of the above cases, were compared with each other, it was found that bone-marrow samples could be sterile when bacteraemia was present, and vice versa (Table III).

TABLE I.—*Result of 106 Blood Cultures from 93 Cases of Brucellosis*

	No.	%
Blood culture positive	74	69·8
,, ,, negative	32	30·2

TABLE II.—*Result of Bone-marrow Cultures from 45 Cases of Brucellosis*

	No.	%
Marrow culture positive	30	66·7
,, ,, negative	15	33·3

TABLE III.—*Result of Simultaneous Blood and Marrow Cultures from 35 Cases of Brucellosis*

Marrow Culture	Blood Culture	No.	%
Positive	Positive	16	45·7
,,	Negative	7	20·0
Negative	Positive	7	20·0
,,	Negative	5	14·3

Blood was collected for culture at random with no reference to the degree of the patient's temperature on the day when the blood was collected or on the days preceding the collection. Each blood sample was collected during the morning, one to two hours after the patient's temperature had been measured and recorded. The relationship between the result of blood culture and the patient's temperature on the day of collection was studied by comparing the result of the blood culture with the morning temperature as well as with the higher of the morning or the evening temperature. When blood was collected for culture more than once from the same patient, only the result of the sample collected on the first occasion was considered.

The results observed in the 93 cases are presented in Tables IV and V, which also show estimates of the number of positive and negative cultures that would

TABLE IV.—*Number of Positive and Negative Blood Cultures Observed in 93 Cases of Brucellosis in Relation to the Morning Temperature on the Day When the Blood was Collected and the Numbers Expected if There Was No Association Between Pyrexia and Bacteraemia*

Temperature Class Intervals		Blood Cultures			
		Positive		Negative	
(°F.)	(°C.)	Observed	Expected	Observed	Expected
97·0– 97·8	36·1–36·6	4	5·59	4	2·41
98·0– 98·8	36·7–37·1	16	20·27	13	8·73
99·0– 99·8	37·2–37·7	20	16·80	4	7·20
100·0–100·8	37·8–38·2	12	11·18	4	4·82
101·0–101·8	38·3–38·8	5	4·19	1	1·81
102·0–102·8	38·9–39·3	3	2·10	0	0·90
103·0–103·8	39·4–39·9	5	4·89	2	2·11
104·0–104·8	40·0–40·5	0	0	0	0
105·0–105·8	40·6–41·0	0	0	0	0
Total		65		28	

Test of significance: $\chi^2 = 7{\cdot}605$ and $0{\cdot}05 < P < 0{\cdot}10$. The first two and the last five classes have been combined.

have been expected to occur if there were no causal relationship between pyrexia and bacteraemia. No significant difference between the observed and the expected numbers has been obtained. Furthermore, cases have occurred where *Br. melitensis* has been recovered from the blood of patients who had been running normal or subnormal temperatures for periods of days or weeks, as in Case 1. It appears that the comparatively large incidence of positive blood cultures at temperatures ranging from 98 to 101.8° F. (36.7 to 38.8° C.) is due to the higher incidence of brucellosis patients presenting at hospital with this range of temperature, be they culturally positive or negative. When blood was collected twice from the same patient the result of the second culture was unpredictable. Table VI shows the results of these cultures with reference to the patients' highest temperature on the day when blood was collected, as well as to the time interval in days from the day of admission to hospital.

The following case is selected for publication because of the prolonged period of bacteraemia without pyrexia.

TABLE V.—*Number of Positive and Negative Blood Cultures Observed in 93 Cases of Brucellosis in Relation to the Higher of the Morning or Evening Temperatures on the Day when Blood was Collected, and the Numbers Expected if There Were No Association Between Pyrexia and Bacteraemia*

Temperature Class Intervals		Blood Cultures			
		Positive		Negative	
(°F.)	(°C.)	Observed	Expected	Observed	Expected
97·0– 97·8	36·1–36·6	1	1·40	1	0·60
98·0– 98·8	36·7–37·1	9	12·58	9	5·42
99·0– 99·8	37·2–37·7	17	18·17	9	7·83
100·0–100·8	37·8–38·2	15	12·58	3	5·42
101·0–101·8	38·3–38·8	9	8·40	3	3·60
102·0–102·8	38·9–39·3	5	3·49	0	1·51
103·0–103·8	39·4–39·9	6	5·59	2	2·41
104·0–104·8	40·0–40·5	1	1·40	1	0·60
105·0–105·8	40·6–41·0	2	1·40	0	0·60
Total		65		28	

Test of significance: $\chi^2 = 6{\cdot}765$ and $0{\cdot}05 < P < 0{\cdot}10$. The first two and the last five classes have been combined.

TABLE VI.—*Result of Cultures from 11 Patients Whose Blood was Drawn and Cultured Twice*

Patient	Days from Date of Admission	Temperature of Patient (°F.)	Temperature of Patient (°C.)	Result of Culture
1	3	100	37·8	+
	6	100	37·8	+
2	3	103	39·4	+
	7	100	37·8	+
3	2	103·4	39·7	+
	3	105	40·6	+
4	3	98·5	36·9	+
	13	98	36·7	+
5	6	99·6	37·6	+
	52	101	38·3	+
6	3	99·4	37·4	–
	11	99·6	37·6	–
7	1	98·5	36·9	–
	7	102·0	38·9	–
8	1	98·5	36·9	–
	4	99·4	37·4	–
9	1	99	37·2	–
	12	98	36·7	+
10	7	104	40·0	–
	3	101	38·3	+
11	2	98·2	36·8	+
	9	100·2	37·9	–

Case Report

A 9-year-old boy attended the out-patient clinic on September 11, 1958, with a history of three episodes of fever to 103° F. (39.4° C.), each lasting about three weeks. The first began in April. After a remission he had developed low-grade pyrexia on September 4, and this had persisted. Serum agglutination with *Br. melitensis* had given negative results on several occasions. There was no history of exposure to infection with brucella. The boy was pale but did not look ill; temperature 99.5° F. (37.5° C.). The spleen was about 3 cm. below the costal arch, firm, not tender; the liver was not appreciably enlarged; lymph nodes were enlarged at the anterior and posterior triangles of the neck, at the axilla, and at the groins; they were discrete, mobile, rather soft, not tender. The largest of these nodes was at the neck. When removed (October 21) it measured 1.7 by 1.8 by 1.2 cm. Histological examination showed only follicular hyperplasia and sinus catarrh. Physical examination was otherwise essentially negative. Chest *x*-ray films showed clear lungs; Mantoux intradermal test was negative at 1 in 1,000 dilution. Paul–Bunnell test, Wassermann reaction, and Kahn test of the blood were negative. Serum agglutination with *Br. melitensis* was positive only at a titre of 1 in 40. This test was repeated after five days with the same result.

The patient was kept in hospital from September 18 to November 10, 1958. From September 21 there was apyrexia, yet *Br. melitensis* was recovered three times from the blood and once from the bone-marrow. The agglutination titre rose, glandular enlargement regressed, and splenic enlargement remained. The child's colour returned soon after admission; his appetite was good and his general condition excellent.

Investigations.—Haematological examination on October 8 showed: haemoglobin, 11.4 g./100 ml.; erythrocytes, 5,110,000/c.mm.; packed cell volume, 38.5%; mean corpuscular volume, 75.5 cubic microns; mean corpuscular haemoglobin, 22.3 $\mu\mu$g.; mean corpuscular haemoglobin concentration, 29.6%. Blood smear showed a moderate increase in central achromia of erythrocytes; polychromasia, stippling, and normoblasts were absent; there was anisocytosis, with a tendency to microcytosis but also with rare macrocytes; poikilocytes rare; reticulocytes 1%. White blood cells numbered 6,650/c.mm. (36% polymorph neutrophils, 6% eosinophils, 1% basophils, 49% lymphocytes, 8% monocytes). No immature leucocytes were seen. A myelogram showed: myeloid, 55.9% (leucoid, 42.2%); and erythroid 7.6%; the myeloid:erythroid ratio being 7.3:1 and the leucoid:erythroid ratio 5.5:1. Total serum proteins were 9 g./100 ml., and the albumin:globulin ratio 2:1. Serum electrophoresis showed an essentially normal pattern. Serum glutamic oxalacetic transaminase was 19 units/ml. (control: 11 units/ml.) and serum glutamic pyruvic transaminase 10 units/ml. (control: 13 units/ml.). Plasma bilirubin, thymol turbidity, and zinc sulphate turbidity were normal.

"Achromycin V" (1 g. daily in four equal doses by mouth from October 22 to November 2) caused bacteraemia to disappear, but splenic enlargement remained. The spleen was still 1 cm. below the costal arch when the patient was seen at the out-patient clinic on December 1, 1958, and January 12 and 26, 1959. After leaving hospital he went to school and played games; yet he remained apyrexial except for an evening temperature of 99° F. (37.2° C.) from December 9 to 12, 1958, and of 100° F. (37.8° C.) on January 1 and 2, 1959. Samples of blood cultured on November 17 and December 1, 1958, were sterile.

Comments

Human brucellosis has protean manifestations. Its onset may be acute or insidious; fever is highly irregular in degree, duration, and course; long remissions may occur; and its symptoms are exceedingly variable in nature and in severity. Diagnosis is derived from agglutination tests with brucella and is confirmed by culture of brucella from the blood-stream, bone-marrow, or other sources. It appears, however, that the occurrence of bacteraemia is as unpredictable as the clinical findings.

The predilection of brucella for the reticulo-endothelial system has been proved by clinical, post-mortem, and experimental studies (Sharp, 1934; Huddleson, 1943; Spink, 1956). Meyer (1943) suggested that continuous bacteraemia might be maintained by focal lesions in bone-marrow. The importance of bone-marrow as a reservoir of brucella can be seen from the fact that brucella can be recovered from bone-marrow with the same facility as blood, as suggested by Tables I and III as well as by the findings of Hamilton (1954), who obtained the same recovery rate of *Br. melitensis* from samples of venous blood as from samples of marrow. Simultaneous blood and marrow samples, drawn by Spink (1956) in the U.S.A. from 59 cases of brucellosis, yielded brucella from the marrow in five cases when bacteraemia was absent, but in no instance was brucella recovered from blood when the marrow sample was sterile. These findings differ from what is reported in Table IV, where blood culture was positive in seven cases from which sterile bone-marrow was drawn. It is therefore suggested that brucella may not be uniformly distributed in bone-marrow and that bacteraemia might be also maintained from other sources as spleen or liver.

The basic tissue reaction to invasion by brucella is granulomatous. Nodular foci have been reported in animals and man; they have been found in spleen, liver, lymph nodes, bone-marrow, etc. The reaction involves macrophage cells with or without the formation of giant cells, as well as plasma cells and lymphocytes. Necrosis is slight or absent, but abscess formation and even caseation may occur (Sundberg and Spink, 1947; Hamilton, 1954; Spink, 1956). Brucella organisms are located intracellularly and may result in a persistent infection for a long time (Spink, 1956). Whatever the factors may be that break the cellular barrier, it would not appear, from what has been reported above, that pyrexia is a sign that the cellular barrier has been broken and that brucella organisms are allowed to roam in the blood.

The pyrexia of brucellosis does not appear to be induced by bacteraemia but by some chemical change connected with the infected tissue cells and influencing the thermo-regulatory centre of the brain. This is supported by the fact that the clinical course of brucellosis is rapidly influenced by treatment with corticotrophin or cortisone, showing an abrupt drop in temperature, though bacteraemia may persist (Spink and Hall, 1952).

Investigations into the possible mechanisms of pyrexia have shown that many bacteria have in their structure lipopolysaccharides of high molecular weight, which, when injected intravenously, cause febrile responses that are preceded by prompt leucopenia (Wood, 1958). With injections that are repeated at intervals of a day or less, a state of tolerance is induced; this state, however, ceases to exist within two weeks after discontinuance of the injections. Further investigations suggest that bacterial pyrogens act upon polymorphonuclear leucocytes, with release of endogenous pyrogen from leucocytes or with alteration of chemical structure of bacterial pyrogen by some action of leucocytes (Snell, 1958). Polymorphonuclear leucocytes appear to have an insignificant role in brucellosis, but it would appear also that the presence of only a minimal number of leucocytes in the blood is necessary for the pyrexial reaction to take place (Cranston *et al.*, 1956). Brucellosis infection which is characterized by leucopenia, and which may present bacteraemia without pyrexia, should offer a fruitful field for the elucidation of the mechanism of pyrexia in man. The significance of leucopenia in brucellosis also merits a careful and detailed study.

Summary

The results of blood and of marrow cultures from cases of brucellosis have been studied. *Brucella melitensis* was recovered from 69.8% of blood cultures and from 66.7% of bone-marrow cultures. Brucellosis bacteraemia is apparently unrelated to pyrexia. Brucellosis should be a fruitful field for the elucidation of the mechanism of pyrexia in man.

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ASCORBIC ACID INHIBITION OF THE GLUCOSE-OXIDASE TEST FOR GLYCOSURIA

BY

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A simple test for the presence of glucose in urine, using the enzyme glucose oxidase, was introduced about three years ago and marketed under the names "clinistix" and "tes-tape." Hunt *et al.* (1956) compared these two products with each other, and with two methods of glucose detection employing reduction of copper sulphate—namely, Benedict's reaction and "clinitest" tablets. They thought both new methods were equally satisfactory as qualitative tests, being as reliable as the copper sulphate reactions and perhaps more sensitive, but they considered tes-tape to be unreliable quantitatively. Like Tunbridge *et al.* (1956), they expressed a preference for clinistix. Luntz (1957), comparing clinistix and clinitest for clinic use, also was impressed favourably with the former.

Clinistix has now come to be used widely as a simple, quick test for glycosuria. According to the manufacturers the test is carried out by dipping the impregnated end of a strip of thick blotting-paper into the urine and noting the presence or absence of a blue colour after an interval of one minute. The end of the paper is impregnated with glucose oxidase, orthotolidine, and vegetable peroxidase. In the presence of atmospheric oxygen, glucose oxidase oxidizes glucose to glucuronic acid and hydrogen peroxide. The latter, in the presence of the peroxidase, gives a blue colour

with orthotolidine. Hunt *et al.* (1956) found that the test is positive if the glucose concentration exceeds 100 mg./100 ml. of urine, but the sensitivity is influenced by *p*H, temperature, and various urinary constituents, of which one may be ascorbic acid. False-positive results due to contamination with traces of hydrogen peroxide or hypochlorites have been reported (Frazer, 1958; Phillips, 1958).

In this laboratory adult urines have been tested for glucose by clinistix, a rough estimate of the amount of glucose present in the positives being obtained by Benedict's test. It caused surprise and concern when it was noticed that clinistix gave negative results in six urine samples obtained during a glucose-tolerance test on a diabetic patient (Mrs. A.), despite blood-sugar levels of more than 200 mg./100 ml. throughout the test. Paper chromatography revealed the presence of glucose, and further investigation suggested that an inhibitor of the glucose-oxidase reaction, such as ascorbic acid, was present. The ascorbic acid concentrations in the specimens of urine from Mrs. A. were estimated and found to range from 120 to 270 mg./100 ml. Subsequently, it came to light that this patient had been given an intramuscular injection of "parentrovite" (a mixed vitamin preparation containing *inter alia* 500 mg. of ascorbic acid in each dose) two hours before the tolerance test and also on the preceding six mornings. These findings, having thrown doubt on the reliability of clinistix, led us to investigate further the value of this test.

Four groups of experiments were performed. Firstly, to study the effect of large doses of ascorbic acid on the detection of glycosuria by clinistix, Mrs. A.'s glucose-tolerance test was repeated after an interval during which vitamin therapy had been withheld, and glucose-tolerance tests were conducted also on other diabetic patients before and after administration of ascorbic acid. Secondly, the degree of inhibition of the glucose-oxidase reaction at various concentrations of ascorbic acid was tested. Thirdly, the excretion of ascorbic acid by healthy adults receiving therapeutic doses was investigated. Finally, a series of routine urine specimens were tested by clinistix and Benedict's reaction in parallel to assess the frequency of discrepancies between the two methods.

Materials and Methods

Blood-sugar Estimations.—The "true sugar" level of capillary blood was estimated by the method of Haslewood and Strookman (1939) except in the case of the first glucose-tolerance test on Mrs. A., in which, at the clinician's request, total reducing substances were estimated by Lehmann and Silk's (1952) modification of Folin and Wu's (1920) technique.

Urine Analysis.—Benedict's reaction and osazone preparation were done by the standard methods. The degree of reduction of Benedict's reagent was indicated by a number of plus signs ranging from one to four. A urine with glucose added to give a concentration of 50 mg./100 ml., which on being tested with Benedict's reagent produced after standing a green supernatant and a definite yellow precipitate, was classified as one plus. One-way chromatography of sugars was carried out on Whatman No. 3 MM paper using an ethyl acetate, pyridine, and water mixture as solvent and benzidine as the location reagent (Smith, 1958). Initially the clinistix test was performed as recommended by the manufacturers, but it was found that full colour development did not always occur in one minute, so throughout this work two minutes were allowed. Low concentrations of glucose, or higher concentrations in the presence of ascorbic acid, produced a tingeing of the edge of the strip (trace) or a pale-blue or mottled appearance (weak positive). A uniform deep blue colour was regarded as positive.

Ascorbic Acid Estimations.—These were performed by the method of Roe and Kuether (1943), in which the ascorbic acid is oxidized to dehydroascorbic acid and the latter estimated.

Glucose-tolerance Tests

1. Mrs. A.'s first tolerance test has been discussed briefly above, and it can be seen (Fig. 1 b) that the renal threshold for glucose was exceeded throughout the test. Clinistix gave a negative result for all six urine specimens whereas Benedict's test was strongly positive. Chromatography confirmed that glucose was present in all the specimens. The volume of the half-hour urine sample was too small for estimation of ascorbic acid, but this substance was found in the five other samples in high concentrations (120–270 mg./100 ml.), Mrs. A. having been given an intramuscular injection containing 500 mg. of ascorbic acid two hours before the test. A second tolerance test (Fig. 1 a) was performed 14 days later, after the vitamin had been withdrawn for 10 days. On this occasion the blood-sugar levels were even higher. Both clinistix and Benedict's tests were positive throughout and chromatography confirmed the presence of glucose in all specimens. On this occasion the urinary ascorbic acid levels ranged from 2.4 to 4 mg./100 ml.

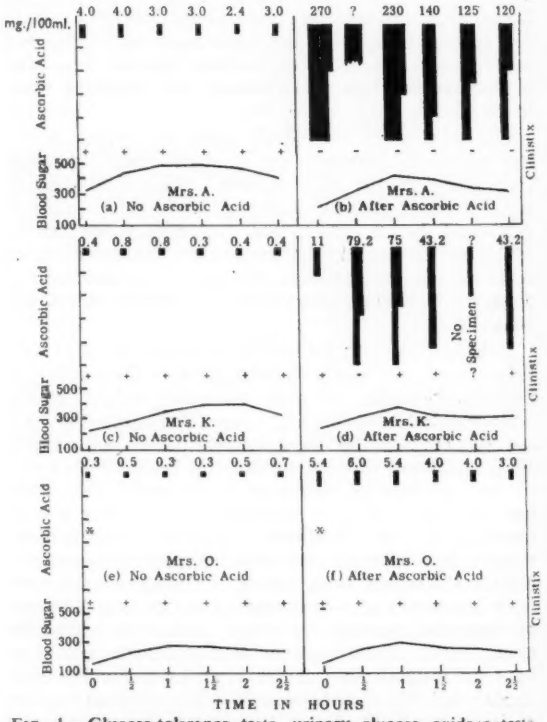

FIG. 1.—Glucose-tolerance tests, urinary glucose oxidase tests, and urinary ascorbic acid levels on three diabetics. Glucose detected chromatographically in all urines. Benedict's test positive in all urines except those marked *.

2. Mrs. K., a known diabetic aged 63, was taken off her insulin before the glucose-tolerance tests were performed. In the first (Fig. 1 c), with blood sugars ranging from 214 to 387 mg./100 ml., clinistix and Benedict's reagent gave positive results and the urinary ascorbic acid levels were 0.4–0.8 mg./100 ml. During her second tolerance test (Fig. 1 d), started two hours after an intramuscular injection of 500 mg. of ascorbic acid, high blood-sugar levels again were present. The ascorbic acid concentrations in the urines were 11, 79.2, and 75 mg./100 ml. at 0, ½, and 1 hour, and 43.2 mg./100 ml. in the 1½- and 2½-hour samples. Clinistix gave a positive result for the fasting sample but was negative in the half-hour specimen, though Benedict's test was positive, and chromatography revealed the presence of glucose. At the end of one hour the ascorbic level had fallen a little but the blood-sugar had risen even further and clinistix was positive again and remained so in the subsequent specimens. All contained glucose when examined by chromatography and gave the expected positive results with Benedict's reagent.

3. Mrs. O., a recently diagnosed diabetic aged 26, had never received insulin. No disagreement between the tests occurred here, but in this case the urinary ascorbic acid levels were only raised from 0.3–0.7 mg./100 ml. (Fig. 1 e) to 3–6 mg./100 ml. by the injection of 500 mg. of ascorbic acid two hours before the test (Fig. 1 f).

Inhibition of Glucose Oxidase by Ascorbic Acid

This was investigated by means of a "checker-board" type of titration in which a block of 14 rows of 14 test-tubes in each row was set up. Pooled urine samples which had been shown to contain negligible quantities of glucose and ascorbic acid were used to make up solutions of glucose and ascorbic acid, and the concentration of glucose was increased from left to right, all the tubes in any one vertical row containing the same amount of the sugar. Similarly, the concentration of ascorbic acid was increased from the bottom to the top, all the tubes in any one horizontal row having the same concentration of the vitamin. Thus the tubes at the bottom left-hand corner contained very small amounts of glucose and ascorbic acid whereas those at the top right-hand corner contained high concentrations. All the tubes, after mixing, were tested with clinistix. The degree of reduction of Benedict's reagent with the different concentrations of glucose, but no ascorbic acid, was noted also.

The composite results of two titrations are illustrated in Fig. 2. A definite positive result was given by clinistix only at a concentration of glucose of 50 mg./100 ml., which is the concentration giving a one-plus reduction of Benedict's solution. Clinistix merely gives a weakly positive or trace reaction with smaller concentrations of glucose. The results show that as little as 10 mg. of ascorbic acid per 100 ml. will inhibit completely the detection of 50 mg./100 ml. of glucose by clinistix and partially inhibit the detection of up to 200 mg./100 ml., so that at the levels of ascorbic acid reached by Mrs. A. during her first glucose-tolerance test, clinistix fails to detect glucose at concentrations of between 250 and 500 mg./100 ml. Such concentrations give a strong reduction of Benedict's solution.

Urinary Ascorbic Acid Excretion by Healthy Adults

In view of the above results, it was decided to seek further information about the quantities of ascorbic acid excreted by healthy adults while on a normal diet, and also after a course of ascorbic acid in normal therapeutic doses. Accordingly random urine samples were collected from 22 healthy adult volunteers, of whom 12 were male. All then took oral ascorbic acid in a dose of 100 mg. t.d.s. for seven days, and on the last day of the course a further random sample of urine was collected from each. Random and not 24-hour collections of urine were chosen deliberately, because the average clinical laboratory has to deal with random samples for routine testing. The ascorbic acid concentrations in these urines were estimated, the results being expressed graphically in Fig. 3.

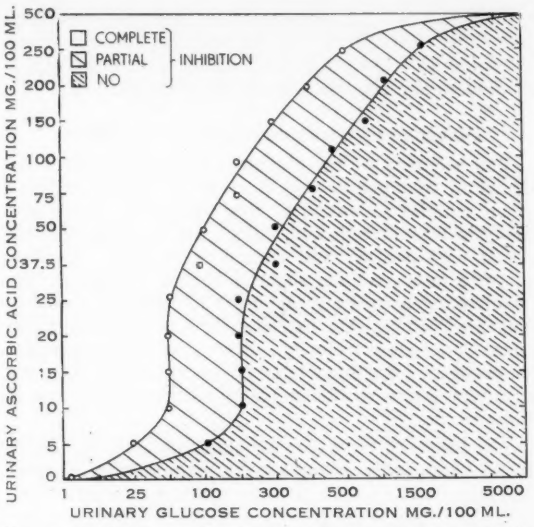

FIG. 2.—Inhibition of the glucose-oxidase reaction by ascorbic acid.

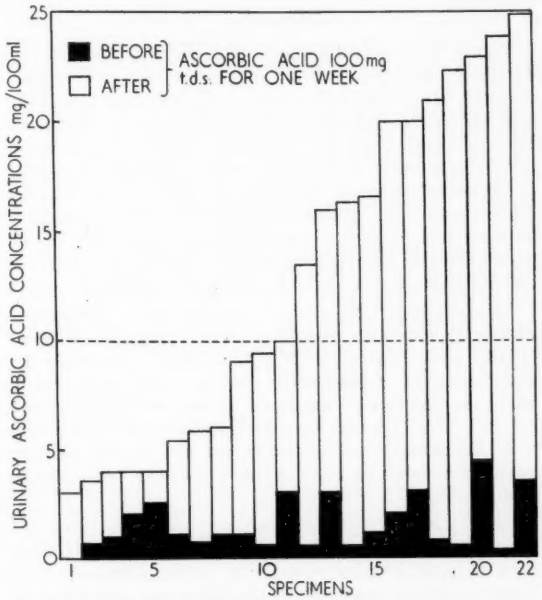

FIG. 3.—Ascorbic acid concentrations in random urine collections from 22 healthy adults. The dotted line indicates the level of ascorbic acid which will inhibit the detection of 50 mg. of glucose per 100 ml.

Just half of the post-treatment samples contained more than 100 mg. of ascorbic acid per 100 ml., which is enough to prevent the detection by clinistix of 50 mg. of glucose per 100 ml. (Benedict's one-plus).

Diagnosis of Glycosuria by Glucose Oxidase

The accuracy of the glucose-oxidase method for the detection of glycosuria in a series of 500 consecutive urine samples submitted to this laboratory for routine analysis was investigated. Each of these urines was tested with clinistix and Benedict's reagent. If either of these tests gave the slightest indication that glucose or any other reducing sugar might be present, an attempt was made to prepare the osazone and to identify the sugar chromatographically. It was not always possible to perform both these tests on every sample, but the sugar, if any, was always identified by at least one of these methods.

The results of these tests are summarized in the Table. In all there were 18 erroneous diagnoses by clinistix (3.6%). In 11 of these the clinistix was positive but no

Survey of 500 Routine Urine Samples by the Glucose-oxidase Test. Glucose Was Identified by Osazone Formation and/or Chromatography

Glucose-oxidase test—positive	37
Glucose-oxidase test positive—glucose present	26
Glucose-oxidase test positive—glucose not detected	11
Glucose-oxidase test—negative	463
Glucose-oxidase test negative—glucose not detected	456
Glucose-oxidase test negative—glucose present	7

Incorrect results, 3·6%

glucose was detected by other tests ; lactose was detected in two of these samples, both from women in the puerperium. (Lactose, of course, even in high concentrations, is not detected by clinistix.) These 11 false positives amount to 2.4% of the total number of urines which did not contain glucose. The clinistix reaction was positive in 26 of the 33 urines that did contain glucose. The remaining seven false-negative results amount to 21.2% of the actual cases of glycosuria in the series.

Discussion

There is no doubt that the clinistix method of detecting glucose in urine possesses many attractive features. It is extremely simple, and therefore variations and errors of technique are reduced to a minimum. Probably this is more important when urine is being tested by a busy nurse in the ward or clinic or by the hard-pressed general practitioner than it is in the laboratory. The major advantages to the laboratory have been the rapidity, sensitivity, and specificity of the tests. On the other hand, its very specificity may be a disadvantage, particularly in paediatric practice.

Furthermore, erroneous results are sometimes obtained with the glucose-oxidase method. Phillips (1958) and Frazer (1958) have both reported the occurrence of false-positive results, and the present study suggests one important cause of false-negative results. The " checker-board " titrations show the extent to which clinistix is inhibited by ascorbic acid in urinary solution, so that cases of frank glycosuria may remain undiagnosed.

The question that demands an answer is how far these erroneous results detract from the value of clinistix as a routine test for glucose in urine. The effect of large doses of ascorbic acid upon the detection of glycosuria is shown in the series of glucose-tolerance tests, Mrs. A.'s being the most striking. Low levels of urinary ascorbic acids were noted in the collections of normal urine, suggesting that the medical students who provided them were largely deficient in the vitamin, and also in many of the series of 22 healthy adults. The rapid rise in 50% of the series to levels of ascorbic acid sufficient to prevent the detection of significant amounts of glucose, after a single week's course of ascorbic acid in therapeutic doses, is of interest. Inquiry has revealed that considerable quantities of vitamin C are given to many patients both in hospital and in general practice ; furthermore, self-prescription of the vitamin in various forms is a practice which is widespread. A further difficulty is that ascorbic acid not only inhibits glucose oxidase but will reduce Benedict's reagent and form crystals with phenylhydrazine which resemble lactosazone.

From the practical point of view, the crux of the matter is the number of erroneous diagnoses that will be made using clinistix, and this is indicated by the results obtained in the short series of routine urine specimens examined in which 21.2% of the actual cases of glycosuria were not diagnosed by clinistix.

Summary and Conclusions

In this work the extent of the inhibition of glucose oxidase by ascorbic acid has been demonstrated, and it has been shown that enough of the vitamin may be excreted after therapeutic doses by mouth or injection to prevent the detection of significant degrees of glycosuria. Furthermore, glycosuria may be incorrectly diagnosed in a significant proportion of routine urine samples submitted to a clinical laboratory if clinistix is used.

While the advantages of clinistix may be recognized, routine testing of urine should be carried out by a less specific method, such as Benedict's test. A urine giving a positive result with Benedict's reagent may be tested further by the glucose-oxidase method for the presence of glucose, but neither negative nor positive results should be regarded as indisputable evidence of the absence or presence of glucose, and, whenever doubt exists, recourse must be had to chromatography or osazone preparation.

We thank Dr. W. H. H. Merivale for his advice and encouragement and for the facilities for this work ; Miss Patricia Bye and Miss Lesley Smith for very able technical assistance ; and Messrs. Ames Co. for the supply of clinistix, and the help they offered us during this investigation. We are grateful to Professor W. J. H. Butterfield, Dr. E. R. Boland, and Dr. J. J. Fleminger for access to patients under their care.

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Between midnight on December 31 and 4 a.m. on January 1 the London Ambulance Service received 159 emergency calls, an average of one call every 1½ minutes. The total number of calls received on New Year's Day was 473—compared with 357, 362, and 386 for the three previous years. (The average number of daily calls received by the service is about 280.)

A CASE OF DISSEMINATED HISTOPLASMOSIS

BY

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Histoplasmosis was first described by Darling (1906) in Panama. No further cases were reported until those of Riley and Watson (1926) in Minnesota and of Phelps and Mallory (1926) from Honduras. Since then the disease has become more widely recognized as a clinical entity, the most common presentation being as a pulmonary infection (Sakula, 1953; Murray *et al.*, 1957; Edge, 1958). It may, however, present as a granulomatous or ulcerating infection of the upper respiratory tract (Parkes and Burtoff, 1949; Roberts and Forman, 1950; Hutchison, 1952; Poles and Lavertine, 1954) or of tongue or oral cavity (Rawson, *et al.*, 1948; Charr, 1953; Locket *et al.*, 1953). In other cases enlargement of the lymph nodes may be the only sign, and practically any type of skin lesion may be mimicked (Derry *et al.*, 1942; Miller *et al.*, 1947; Symmers, 1956). The primary pulmonary form of the disease has an excellent prognosis, but the localized forms are more serious and the disseminated type is often fatal (Price, 1956). In the disseminated disease a predilection is shown for the reticulo-endothelial system—that is, lymph nodes, liver, and spleen—and the adrenals, mucosal surfaces, and skin are also often involved. Brain and bone are rarely affected, however, and the kidney is generally spared (Schwarz, 1956).

Not until the introduction of the histoplasmin skin test (Palmer, 1945) and its use in conjunction with *x*-ray examination of the chest was it realized that a benign subclinical form of the disease also existed. As a result of surveys, it was established that an endemic area exists in the U.S.A. centred on the lowlands around the junctions of the Missouri, Mississippi, and Ohio Rivers. It has been estimated that between 20 and 30 million people in the U.S.A. have at some time been infected with histoplasmosis (Silverman *et al.*, 1955). Though the histoplasmin skin test is not entirely specific and weak reactions may result from cross-reaction with other fungal infections (Mochi and Edwards, 1952; Edwards *et al.*, 1956), the acceptance of strict criteria of positive reactions enables it to be of great value in surveying possible endemic areas. With regard to India and Pakistan, there would appear to be no evidence of histoplasmin skin sensitivity in the surveys so far carried out, provided that definite criteria are observed (Edwards *et al.*, 1956).

The disease is the result of infection by the fungus *Histoplasma capsulatum*, which exists dimorphically as a hyphal saphrophytic form and an encapsulated yeast-like spore form. Infection from natural sources is probably due to the mycelial phase, and the portal of entry may be the respiratory tract, the alimentary canal, or through the skin. When the disease becomes established, however, it is the yeast-like phase which invades the tissue cells. Fuller descriptions of various aspects of the disease can be found in the Proceedings of the Conference on Histoplasmosis, 1952 (Schwarz, 1956); and in the papers of Parsons and Zarafonetis (1945), Mochi and Edwards (1952), Silverman *et al.* (1955), Edwards *et al.* (1956), and Symmers (1956) amongst others.

Symmers (1956), speaking of Britain and discussing all forms of the disease, said: "Histoplasmosis has seldom been recognized in this country, where it is looked upon as an exotic disease and consequently has attracted little attention." Of the 15 cases so far described in Britain, three have been of the disseminated type. A fourth case of this type is presented below.

Case Report

The patient, a 62-year-old Englishman, was admitted to this hospital on April 6, 1958. He had spent the previous 30 years in India, the first half doing afforestation work centred on Karachi, the second in a Calcutta office. He had been a healthy athletic man, keen on climbing, and a fairly heavy drinker. His main complaints on admission were of a loss of 4½ stone (28.6 kg.), anorexia, and great lassitude. He dated his symptoms from an attempt to slim eight months previously (August, 1957), when on medical advice he had taken dexamphetamine sulphate tablets for a few weeks. On ceasing to take them his appetite failed to improve and he felt generally unwell. Two months after this (late September, 1957) he consulted a medical specialist in London, who noted dyspnoea on effort and an odd mental state, in that he described doing things which he had not done. His liver and spleen were just palpable and he had albuminuria. His blood-pressure was 120/80 mm. Hg.

He returned to India and in December, 1957, consulted a surgeon about an ulcer on his tongue. In February, 1958, this was excised and at the same time a small mass of granulation tissue, which had appeared around the anus, was also removed. Both sites healed well. Histologically the tongue lesion was described as a granular-cell myoblastoma and the anal lesion as non-specific granulation tissue. His general health continued to deteriorate, the loss of weight becoming ever more rapid and the lethargy and mental state giving rise to great anxiety for his sanity.

He returned to London in April and was admitted to hospital. At this time he was so drowsy that it was difficult to obtain a history. He had slight fever and appeared anaemic, but there was no abnormal pigmentation of his skin or mucous membranes. He had obviously lost weight, but was by no means wasted (weight 11½ stone; 73 kg.). A healed scar was present on the dorsum of his tongue. Both liver and spleen were just palpable, but otherwise no abnormal physical signs were elicited. His blood-pressure was 120/80 mm. Hg.

Because of the anorexia and loss of weight, carcinoma of the stomach was suspected, but a barium-meal examination showed no abnormality of his gastro-intestinal tract apart from some colonic diverticulosis. A chest *x*-ray examination made at the same time revealed no abnormality of his heart, aorta, or lungs.

His haemoglobin concentration was 8.8 g./100 ml. (60%) and the white-cell count 3,000/c.mm. (neutrophils 51%, lymphocytes 44%, monocytes 2%, eosinophils 3%). During the next nine weeks the haemoglobin concentration only once exceeded 10.4 g./100 ml., and his anaemia was always of the normochromic normocytic type. The average of the nine estimations done was 9.6 g./100 ml. The total white-cell count was usually low (3,000–4,000/c.mm.), only once reaching 8,000/c.mm., and apart from the first two counts always showed a neutrophil preponderance (more than 80%).

The erythrocyte sedimentation rate was always raised, the highest reading being 56 mm. in the first hour and 95 mm. in the second (Westergren). Sternal marrow taken two weeks after admission showed no abnormality apart from some increase in the number of eosinophil myelocytes.

The empirical tests of liver function were all abnormal at the time of admission (thymol turbidity 5 units, thymol flocculation 2+, serum colloidal gold 2+, zinc sulphate turbidity 12 units, ammonium sulphate turbidity 4 units). This was thought to be probably connected with his alcohol consumption. The total serum protein concentration was 6.2 g./100 ml., the A/G ratio being 1.48.

Clinically his condition remained unchanged during the first week, the low-grade fever continuing with occasional spikes of temperature up to 100.8° F. (38.2° C.). One week after admission, however, his condition suddenly deteriorated and he became more drowsy, was confused, had hiccups, exhibited muscle twitchings, and had an unpleasant oral fetor. His blood urea was found at this time to be 165 mg./100 ml., serum sodium 140 mEq/l., potassium 5.9 mEq/l., chloride 107 mEq/l., and alkali reserve 20 mEq/l. (Fig. 1). He had had slight proteinuria (about 50 mg./100 ml.) since admission, and a urine specific gravity greater than 1007 had never been obtained. No casts, cells, or organisms were found in the urine at this time, and the daily output was at least a litre. The *p*H was always on the acid side of neutrality. This combination of high serum urea and potassium, with a urine of reasonable volume but low specific gravity and containing albumin, suggested a renal lesion, and since his blood urea five months previously was 26 mg./100 ml. it seemed that such a lesion must have been of recent onset or sudden deterioration.

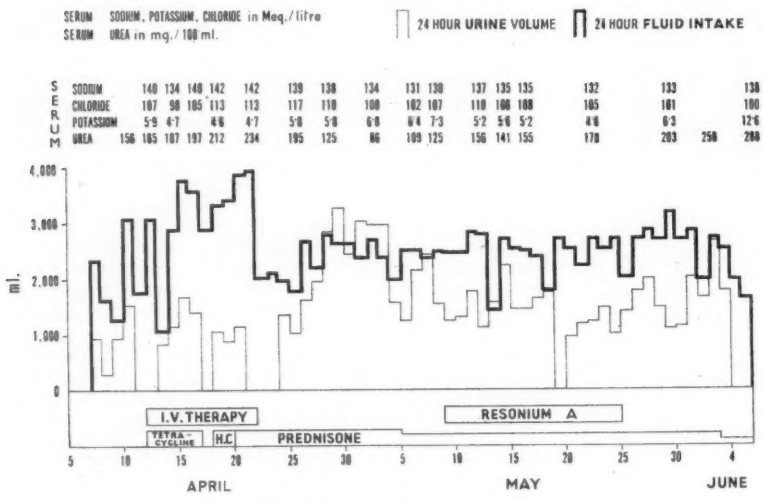

FIG. 1.—Showing electrolytes and fluid balance.

As the symptoms, clinical state, and laboratory findings were compatible with either renal or hepatic failure, he was put on a routine of intravenous 10% dextrose together with a diet very low in protein, and 0.25 g. of tetracycline six-hourly by mouth. This latter was discontinued after five days because of diarrhoea and anal excoriation. The temperature settled at this time, and from then on was subnormal, frequently being as low as 95–96° F. (35–35.6° C.). The intravenous therapy was continued for 10 days, and during this time the serum potassium level fell to 4.7 mEq/l., presumably because of a shift from the extracellular to the intracellular fluids. The blood urea level, however, rose ever higher to a maximum of 234 mg./100 ml. on the tenth day. The serum sodium and chloride levels remained normal. The daily urine output at this time continued to be good, but the urea concentration was only 0.95 g./100 ml. The chloride concentration was 38 mEq/l. or 2.2 g./l. as sodium chloride.

His general condition did not improve on this regime, and by now some more generalized disease process, such as disseminated lupus erythematosus, was being postulated in an attempt to explain the hepatosplenomegaly, abnormal mental state, leucopenia, raised erythrocyte sedimentation rate, and abnormal biochemical tests. No L.E. cells could be demonstrated in his circulating blood, but, in view of his critical state, it was decided to start steroid therapy. 100 mg. of hydrocortisone was therefore added to the intravenous infusion for two days, followed by oral prednisone in a dose of 10 mg. eight-hourly.

On this regime there was a dramatic clinical improvement, which was maintained for the next three weeks. He became mentally clear, alert, and communicative. The liver and spleen ceased to be palpable, and the empirical liver-function tests became negative and remained so. The prednisone induced a diuresis—urine volumes around 3 litres a day being produced. His blood urea fell rapidly from its level of 234 mg./100 ml. at the start of steroid therapy to 86 mg./100 ml. a fortnight later, before starting to rise again. The serum sodium and chloride levels were also reduced to their lowest values, being 130 mEq/l. and 100 mEq/l. respectively at this stage.

Though the urea content of the urine was still low at 0.58 g./100 ml. and the sodium and chloride contents slightly low at 52 mEq/l. and 55 mEq/l. respectively, it was felt that the diuresis was sufficient to account for these values.

It was difficult to explain, except by postulating increasing cell damage, the serum potassium level, which steadily rose from 4.7 to 7.3 mEq/l. after three weeks of steroid therapy, despite a good urine potassium content of 27 mEq/l. An attempt was made to check this rise, by removing foods high in potassium from the diet and later by giving "resonium-A," 15 g. t.d.s. This controlled the serum potassium in the 5 mEq/l. region while it was given. The blood urea continued to rise, finally reaching 288 mg./100 ml.

On two occasions he had a trace of blood in the urine, and on May 16 (three weeks before death and a month after starting steroid therapy) he had the first of several attacks of frank haematuria. Because of the serum urea concentration an intravenous pyelogram was never feasible. Cystoscopy was performed, but no abnormality was found in the bladder, and ureteric catheters could not be passed.

Haematuria became persistent and gross, and despite blood transfusion he gradually went downhill and died on June 6, nine weeks after admission. In the last week of his life prednisone dosage had been reduced to 5 mg. t.d.s. and the resonium-A discontinued. On the day of death the serum potassium was 12.6 mEq/l. and the serum urea 288 mg./100 ml.

Necropsy Findings

There was no increased pigmentation of the skin, nipples, anus, or oral cavity. The brain (1,280 g.) was macroscopically normal. On the dorsum of the tongue there was

a recurrence of the ulcer 1 cm. in diameter. The gastro-intestinal tract was normal and there was no recurrence of the anal granuloma. There were no lesions of the lungs or bronchi. The heart (395 g.) had been arrested in systole (interesting in view of the high serum potassium level which is said to cause arrest in diastole). There was moderate hypertrophy of the left ventricular myocardium. The liver (2,495 g.) was enlarged and finely nodular. The cut surface showed the appearances of a multilobular type of cirrhosis

FIG. 2.—Kidneys and adrenals, showing gross adrenal destruction and extensive lesions of renal medulla.

with dilatation of some of the bile-ducts, which appeared occasionally as small cysts. The spleen (760 g.) was enlarged and firm, with a normal architecture.

The *adrenals* were replaced by large tumour-like swellings (Fig. 2); that on the right was roughly spherical (8–9 cm. in diameter); that on the left more oblong (13 by 8 by 7 cm.). The cut surface of each showed considerable amounts of yellowish necrotic material within fairly thin fibrous capsules. There was an occasional thickening of the capsule by firm white tissue measuring up to 3 cm.

FIG. 3.—Kidney, showing typical lesions of renal medulla.

The *kidneys* were of normal size and contour. Cut surface revealed, confined to the medullary region, several circumscribed, almost spherical lesions greyish-white in colour, with streaks of haemorrhage and areas of necrosis (Figs. 2 and 3). Small miliary foci could also be seen and there was a streaky effect in the line of the medullary rays.

The most likely diagnosis appeared to be tuberculosis, but the lesions did not show true caseation, and aroused sufficient curiosity for a frozen section to be done, as a result of which the diagnosis of histoplasmosis was established.

It was now realized that the ulcer of the tongue removed in India could have been due to histoplasmosis. The original blocks of the tongue ulcer and anal lesion were obtained, and this fact was confirmed.

Serum taken on the day of death and refrigerated was sent to Dr. R. W. Riddell for complement-fixation tests, but proved anti-complementary. The blood clot was cultured in various suitable media, but no growth was obtained.

Histology

The characteristic picture in the sections of the granuloma of the tongue and anal region, and in the lesions in the adrenal and kidney, was of great accumulations of macrophages containing vast numbers of intracellular histoplasmas. None of the macrophages was multinucleated, though an occasional binucleate form was found.

The histoplasmas (Fig. 4) were so abundant that they were easily visible in haematoxylin-and-eosin-stained sections at low magnification. They were of relatively uniform size, oval in shape (about 4 by 2 μ), with a double contour external wall. They were best demonstrated by the periodic-acid/Schiff technique, when a central granular pink-staining chromatin mass could be identified, with a clear zone between it and the external wall. Most of the organisms were birefringent. They were not so clearly demonstrated by Gridley's stain as by P.A.S. These appearances were exactly similar to previous descriptions of histoplasmas, as was their peculiar confinement to macrophages. The organisms were larger than those of leishmania, and, unlike them, had caused considerable cell destruction.

In the adrenal tumours the heavily parasitized macrophages were collected together in islands surrounded by large areas of necrosis, in which were vast numbers of free histoplasmas. These were not as conspicuous as their intracellular counterparts, many staining poorly and appearing

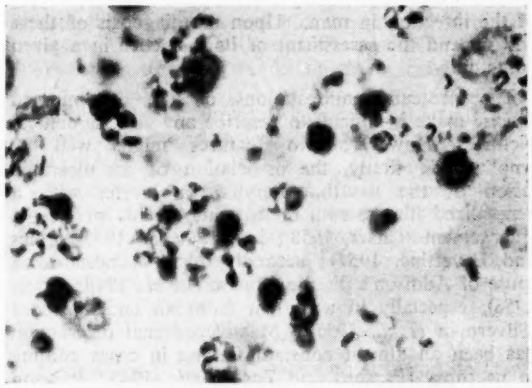

FIG. 4.—Typical microscopical appearance of macrophages with intracellular histoplasmas. (×1,600.)

to be disintegrating. Only an occasional microscopic focus of surviving adrenal tissue was found.

The large lesions in the renal medulla were of a similar nature and had caused much destruction of tissue. The miliary lesions were some 2–3 mm. in diameter and consisted of an outer zone of macrophages and histiocytes surrounding an area of early necrosis, in which a few polymorphonuclear cells could be identified. The macrophages in these lesions contained very few histoplasmas, and the histiocytes only an occasional single organism.

No histoplasmas were found in the liver or spleen despite the examination of numerous sections using special staining techniques. In the liver the changes of a multilobular type of cirrhosis were confirmed, and it was presumed that this had an alcoholic aetiology and was not related to histoplasmosis.

Discussion

The possible association of histoplasmosis with residence in India seems worthy of reiteration. In two of the three fatal cases previously reported in Britain, also in Hutchison's laryngeal case, the patients had all lived there for varying periods, and it would seem that it was in India that the present patient acquired his infection. Though only one report of a case actually diagnosed in India has been found (Panja and Sen, 1954) the possibility of histoplasmosis, both in Indian patients and in those who have lived in that country, should be considered when appropriate.

Diagnosis is best established by culture of the organisms from biopsy material, blood, bone-marrow, sputum, or gastric washings, and is preferable to merely seeing them microscopically in these materials (Silverman *et al.*, 1955). The histoplasmin skin test is probably clinically analogous to the Mantoux test in tuberculosis. Serological methods include various complement-fixation and agglutination tests, and as these become positive at different stages of the disease (Campbell, 1958) they are best employed altogether at any one time. Biopsy has been said to precipitate dissemination of the disease, but Symmers (1956) believes that this danger may be exaggerated. His three patients were still alive and well, three years after biopsy, without any evidence of dissemination of the disease (Symmers, 1959, personal communication).

It is not within the scope of this paper to discuss in detail the localized lesions or pulmonary forms, though these undoubtedly form by far the major part of the infection in man. Upon the diagnosis of these will depend the assessment of its incidence in a given community.

The protean manifestations of the disseminated disease make it difficult to describe any concise clinical picture. However, two features might well be emphasized: firstly, the association of an ulcerated lesion of the mouth, pharynx, or larynx with a generalized illness, with or without hepatic or splenic enlargement (Charr, 1953; Locket *et al.*, 1953; Poles and Lavertine, 1954); secondly, histoplasmosis as a cause of Addison's disease (Rawson *et al.*, 1948; Price, 1956), especially in a patient from an endemic area (Silverman *et al.*, 1955). Massive adrenal destruction has been an almost constant finding in cases coming to necropsy (Parsons and Zarafonetis, 1945; Rawson *et al.*, 1948), and, though some equivocal signs which could be associated with adrenal insufficiency have commonly been present, a full Addisonian state is rare, manifestations of disease elsewhere usually being dominant, as in the present case. With regard to the first of these points, had the importance of the tongue ulcer been realized, the diagnosis might have been established in life. Regarding the second, the difficulty in diagnosing the Addisonian state has been demonstrated. The normal sodium and chloride levels in the serum and urine, together with the absence of clinical evidence of adrenal insufficiency, militated against the diagnosis of Addison's disease—the high serum urea and potassium concentrations and the low urine urea concentrations being ascribed to a renal lesion, this supposition being borne out by the constant low specific gravity of the urine and the presence of albuminuria and haematuria.

The mental condition of the patient is not likely to have been the direct result of the infection, as after death no abnormality was discovered in the nervous system such as the granulomatous basal meningitis reported in a disorientated patient by Sprofkin *et al.* (1955). However, it may well have been related to his presumably alcoholic cirrhosis, the improvement resulting from prednisone being analogous to the temporary improvement reported in some cases of hepatic coma (Webster and Davidson, 1957; Pessar and Hessing, 1958). The reversion of the empirical liver-function tests to normal at this time seems to bear this out.

Compared with other reported cases coming to necropsy, our case had two unusual features: (1) the failure to find any evidence of infection in the liver and spleen despite the study of many sections with special staining techniques; and (2) the extensive involvement of the kidneys, especially the medullary region.

Until recently the treatment of histoplasmosis, like that of the other systemic mycoses, has been unsatisfactory (Furcolow, 1958); but a new agent, amphotericin B, an antibiotic derived from a species of *Streptomyces*, has been found to give promising results. It is most effective when given intravenously and is usually free from serious side-effects, though headache, febrile reactions, local phlebitis, and temporary renal impairment have been reported (Appelbaum and Shtokalko, 1957; Rubin *et al.*, 1957; Biddle and Koenig, 1958; FitzPatrick *et al.*, 1958; Greendyke and Kaltreider, 1959).

When there is evidence of adrenal failure the administration of cortisone is hazardous, as it may accelerate the disease process despite an initial period of apparent improvement (Silverman *et al.*, 1955). This fact may be the explanation of the paradoxical rise of serum potassium in our case when the serum urea was falling during the administration of prednisone. The concurrent administration of a potent antifungal drug with the adrenal steroid may allow the correction of the Addisonian state without undue hazard.

Summary

The fourth case of disseminated histoplasmosis reported in Britain is described.

The patient, who had lived in India for 30 years, was a man aged 62 who presented with loss of weight, anorexia, and lassitude of eight months' duration. Two months after the onset of symptoms, granulomatous lesions were removed from his tongue and anal regions. These were at first misinterpreted histologically, but review of the sections in the light of the post-mortem findings showed that they were histoplasmic granulomas.

Interesting features of the electrolyte disturbances are discussed.

Necropsy revealed gross destruction of the adrenals and considerable involvement of the kidneys due to *Histoplasma capsulatum*.

We thank Lord Evans, under whose care the patient was admitted, for permission to publish this case. Our thanks are also due to Professor W. St. C. Symmers for much helpful criticism and advice in the preparation of

this paper, and to Dr. R. W. Riddell for the complement-fixation tests.

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In 1959 the Society of Public Health Educators in America published three additional monographs in their series, Numbers 4, 5, and 6. Number 4, by Dr. W. Griffiths (University of California), is "Health Workers' Attitudes toward Community Development Programs"; in Number 5, Dr. Cora DuBois (Harvard University and Radcliffe College) reconciles the theories of anthropologists, sociologists, and psychologists as they relate to socio-cultural change. Also in Number 5 is an appraisal of operational research in health education by Dr. K. D. Benne (Boston University). Number 6 contains three articles: "Motivation—Some Basic Psychological Issues," by Dr. Richard S. Lazarus (University of California); "Motivation in Small Groups," by Dr. Edmund H. Volkart (Stanford University); and "Power and Participation in the Local Community," by Dr. William Kornhauser (University of California). Further details are available from the Society of Public Health Educators, Office of the Monograph Committee, 121, East 11th Street, Oakland, California, U.S.A.

STUDIES ON THE HAEMOGLOBIN OF NEWBORN NIGERIANS

BY

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In studies of diseases caused by inheritance of the abnormal haemoglobins, in particular haemoglobin S, the presence of foetal haemoglobin in the erythrocytes during the first few months of life interferes with early determination of the haemoglobin genotype of individuals (using the standard techniques as present in general use). As a result sickle-cell anaemia and its genetic variants have not been detected at birth or during the first three months of life, and consequently this gap in our knowledge of the natural history of these diseases remains to be filled. It has also been impracticable to include the neonatal period in investigations on the population dynamics of the sickle-cell gene. It is not inconceivable that factors which operate during this period might lie behind some of the riddles presented by sickling frequencies in populations.

In March, 1958, it was decided to investigate the haemoglobins of babies at birth and to follow up these cases for six months in order to get an idea of the changing pattern of the haemoglobin content of the erythrocytes. We hoped that the pattern of results of the standard tests employed might point a way to earlier definitive diagnosis of diseases caused by the abnormal haemoglobins.

The object of this communication is to present the results of some of our investigations, in particular our findings on filter-paper electrophoresis of the haemoglobin, which in a number of cases yielded unexpected and unusual results.

Material and Methods

The subjects in this investigation were 100 babies born at University College Hospital, Ibadan. The only criterion for inclusion was that a sample of cord blood was obtained at delivery. Subsequently, samples of blood were collected monthly at the post-natal clinic. Unfortunately, a large proportion of cases defaulted from follow-up, and in many cases our investigations are incomplete. Table I shows the follow-up achieved.

TABLE I.—*Number of Cases Attending Monthly Follow-up*

	Birth	1 Month	2 Months	3 Months	4 Months
No. of cases ..	100	50	29	18	4

(1) Sickling tests were done using freshly prepared 2% sodium metabisulphite. (2) Foetal haemoglobin

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estimations were done using the one-minute alkali-denaturation technique of Singer *et al.* (1951). (3) Filter-paper electrophoresis of the haemoglobin was carried out with the hanging-strip method, using barbitone buffer at *p*H 8.6 ionic strength 0.05. (4) Erythrocyte osmotic fragility tests were done using technique described by Dacie (1954).

Results

Sickling was detected at birth in only five cases, the foetal Hb content being 50%, 70%, 89%, 80%, and 66.4% respectively. In six other cases sickling, while undetected at birth, became evident during the next two months. The foetal haemoglobin at birth in this group ranged from 72 to 86%. All sickling preparations were checked by at least two and usually three of us. Of these 11 sicklers, seven have proved to be sickle-cell-trait carriers, one appears to be a case of sickle-cell haemoglobin C disease (sickling was first detected at 2 months of age in this case), and in the remaining three the genotype could not be accurately determined owing to lack of follow-up.

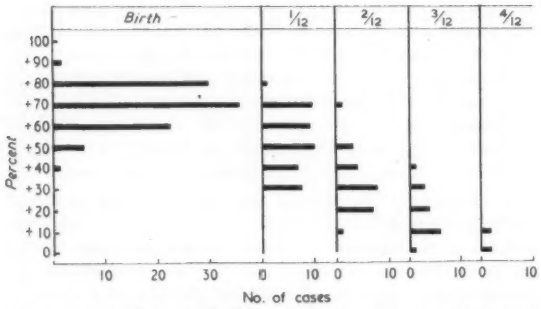


FIG. 1.—Foetal haemoglobin estimations in 100 cases at birth and in a proportion of these at monthly intervals for four months.

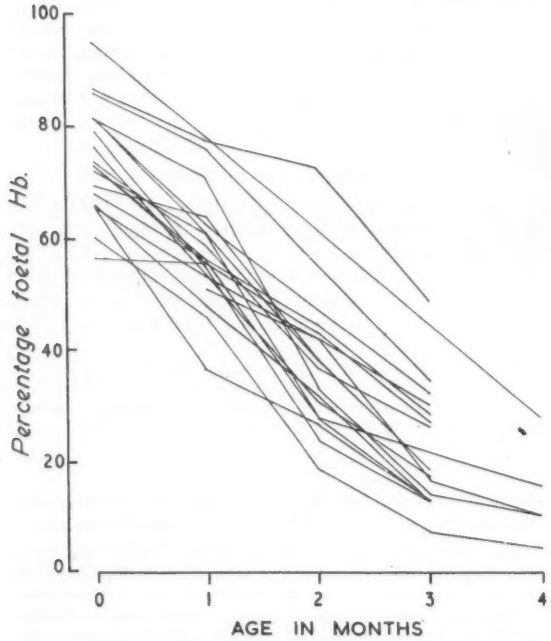


FIG. 2.—Serial foetal haemoglobin estimations in 18 cases, plotted to show the rate of fall in individual cases.

Foetal Haemoglobin Estimations.—Fig. 1 shows all the estimations carried out on the first series of 100 cases. It will be seen that at birth most of these cases had a foetal haemoglobin percentage of 70 or more; however, there was a wide range from 45 to 96%. In subsequent months there was a progressive fall, and by four months some patients had lost most of their foetal haemoglobin. Fig. 2 shows the rate of fall of foetal haemoglobin in 18 cases month by month. It will be seen that in general the decline of individual cases follows the pattern of fall indicated in Fig. 1.

Filter-paper Electrophoresis

As was to be expected, the presence of foetal haemoglobin obscured the true adult haemoglobin pattern at birth and during the early months. Haemoglobin A moves faster than F and the latter faster than S at *p*H 8.6, but the difference in their mobility is not great enough to get clear separation on electrophoresis. Haemoglobin C, however, moves very much slower than A, F, or S, and even at birth can be identified with certainty. Case 27, with 60% foetal haemoglobin, showed haemoglobin C at birth. As things stand at present, using the standard techniques, it is not always possible to diagnose the adult genotype at birth except possibly in the case of sickle-cell haemoglobin C disease. When sickle cells are present at birth haemoglobin S is certain to be found; if the same case shows a percentage of haemoglobin C on electrophoresis, the diagnosis of sickle-cell haemoglobin C disease can be made with certainty.

A completely unexpected finding on electrophoresis was the presence of fast-moving haemoglobin components in 11 of the 100 cases investigated. Out of 40 new cases recently investigated 4 were found to have such a component.

Among the cases showing fast-moving haemoglobins were uniovular twins. Fig. 3 shows the electrophoretic pattern in these children at birth and subsequently.

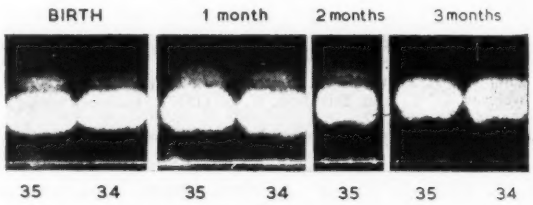


FIG. 3.—Serial paper electrophoresis of the haemoglobin at monthly intervals in Cases 34 and 35, showing the gradual disappearance of the abnormal fast-moving haemoglobin component.

It will be seen that the abnormal fraction persisted for the first two months and then disappeared at the third month.

Table II shows sex, birth weights, foetal haemoglobin estimations, and genotypes in the children concerned and also the maternal blood groups, genotypes, and tribal origin. It would appear that "fast-moving" haemoglobin is unrelated to any of the details listed. It is of interest to note that erythrocyte osmotic fragility tests performed on two of the cases showed a greatly reduced osmotic fragility in both. Fig. 4 shows the osmotic fragility curves in these cases.

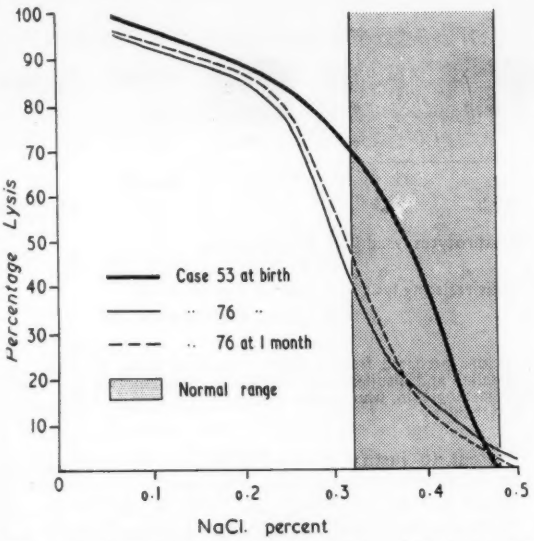


FIG. 4.—Erythrocyte osmotic fragility curves obtained in two cases which showed the abnormal fast-moving haemoglobin component.

Discussion

Our failure to detect sickling at birth in some infants who later showed it accords with the experience of others. Diggs *et al.* (1933) found sickling in only 6 out of 159 newborn American negroes, an incidence of 3.8%, compared with an incidence of 8.3% among 2,539 negroes of all ages. Sharp and Schleicher (1936) report an instance in which sickling was not detected at birth but was present at 4 months. On the other hand, Watson *et al.* (1948), in their series of 226 mothers and babies, found sickling in 8% of the mothers and 8.4% of the babies. Our foetal haemoglobin estimations show that the failure to demonstrate sickling in some cases was not related to the quantity of foetal haemoglobin present. The range of values obtained in these cases was similar to that found among cases which showed sickling. The reason for our failure sometimes to detect sickling might be technical, but we think this is unlikely, as scrupulous attention to detail was always observed. Sickling preparations were made from cord blood, while in the series reported by Watson *et al.*, heel-prick samples were used. It seems reasonable to postulate that differences in the results of sickling tests at birth in their series and ours might be related to the source of origin of the samples tested.

Our results of foetal haemoglobin estimation are in agreement with those reported by others (Jonxis, 1948; Chernoff and Singer, 1952). Chernoff and Singer have shown that, while there is a sharp decline of foetal haemoglobin during the first six months of life, substantial amounts may persist until the end of the first year of life, and traces may persist for three to four years. In some cases the mechanism for production of foetal haemoglobin may never be lost. This usually happens in certain congenital haemolytic disorders, notably thalassaemia and sickle-cell anaemia (Liquori, 1951; Chernoff and Singer, 1952; Itano, 1953). Occasionally foetal haemoglobin may reappear during the course of some acquired blood dyscrasia (Singer *et al.*, 1951; Itano, 1953) and has also been detected in molar pregnancies (Bromberg *et al.*, 1957).

The production of foetal haemoglobin is under a different genetic control from adult haemoglobin. This is shown by the fact that foetal haemoglobin is present in all infants irrespective of their adult haemoglobin genotype. Foetal haemoglobin differs from adult haemoglobin in its crystal form, solubility, immunological behaviour, electrophoresis, spectral absorption, amino-acid composition, and resistance to alkali denaturation (Wintrobe, 1956).

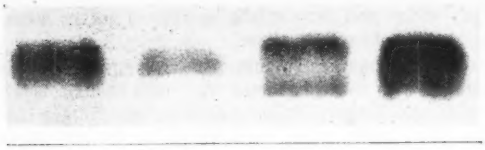
It remains to be shown whether foetal haemoglobin occurs in a mixture with adult haemoglobin in individual erythrocytes or whether there are two distinct cell populations. The fact that at birth only a small percentage of red cells show sickling indicates that there is a qualitative difference in the haemoglobin of individual cells. Further, the rate of increase in the percentage of sickled cells observed during the first four months of life (Watson *et al.*, 1948) bears an inverse relation to the percentage of foetal haemoglobin found during the same period in our cases and in those reported by others (Chernoff and Singer, 1952). This observation has been confirmed by Shields *et al.* (1958). These observations imply that there are two cell populations—one containing foetal haemoglobin and the other adult haemoglobin, the latter gradually replacing the former during the first few months of life.

Case 2 in the present series showed sickling at birth, and we attempted to separate S-containing cells from F-containing cells by lysing the erythrocytes in varying

TABLE II.—*Some Particulars Relating to Babies Showing Abnormal "Fast-moving" Haemoglobin at Birth*

Baby							Mother		
No.	Sex	Birth Weight lb. oz.	Birth Weight g.	Sickling	% Hb F	Genotype	Blood Group	Genotype	Race
9	F			—	72·2	A/A	A.Rh+	A/A	Yoruba
29	F	6 15	3,175	?	84·3	?	O.Rh+	A/A	Ibo
33	M			—	69·0	A/A	B.Rh+	A/A	Yoruba
34*	F	6 7	2,920	—	76·7	A/A	A.Rh+	A/A	Yoruba
35*	F	6 8	2,950	—	73·5	A/A			
40	M			—	78·8	A/A	O.Rh+	A/A	,,
43	F	6 7½	2,935	—	65·7	A/A	A.Rh+	A/A	,,
47	F			—	78·9	A/A	B.Rh+	A/A	Tsekiri
53†	M	Premature		—	94·6	A/A	A.Rh+		Yoruba
63	F	5 11	2,580	+ at 2/12	86·0	S/C			,,
76†	F			—	70·1	A/A	B.Rh+		Ghanaian
				New Series Started In November, 1958					
107	F	6 5	2,865	+	66·6		O.Rh+	A/S	Yoruba
106	F	7 13	3,545	—	65·0		O.Rh+	A/A	,,
125	F	6 1½	2,764	—	77·2		O.Rh+		,,
137	F	5 1	2,295	—	75·0		O.Rh+	A/S	,,

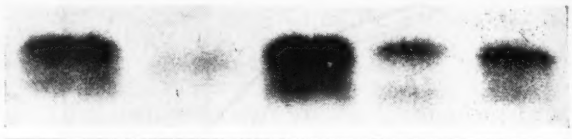
* Twins. † Erythrocyte osmotic fragility reduced.



a.	b.	control	c.
AFS	F	AS	AFS

a. Erythrocytes lysed with distilled water
b. „ „ „ 0.25 N. saline
c. Cells resisting lysis in b. lysed in distilled water.

FIG. 5



c.	b.	a.	control	d.
AFS	F	AFS	AS	AS+Little F

a. Erythrocytes lysed with distilled water.
b. „ „ „ 0.35 N. saline.
c. Cells resisting lysis in b. lysed in 0.25 N. saline
d. „ „ „ „ c. „ „ distilled water.

FIG. 6

FIGS. 5 and 6.—Showing paper electrophoresis on haemoglobin solutions prepared from a single sample of blood of Case 2 at one month (left) and two months (right), using different strengths of saline and distilled water to obtain the haemolysates. It will be seen that solution (b) in each case consists almost entirely of foetal haemoglobin, whereas the other solutions contain a mixture of haemoglobins A, S, and F.

strengths of saline according to a technique previously described by one of us (Hendrickse, 1958). We presumed that the F- and S-containing cells would show differential lysis. Our results, shown in Figs. 5 and 6, offer direct support for the concept of separate cell populations. In sickle-cell anaemia, however, in which as much as 20% of the haemoglobin may be foetal in type, all the erythrocytes can be induced to sickle under optimum conditions (Singer *et al.*, 1951). It must be concluded, therefore, that in this condition sickle and foetal haemoglobin occur together in individual erythrocytes.

We have at present no indication of the significance of the fast-moving haemoglobin components we have found. The rate of disappearance indicates a relation to foetal haemoglobin. The occurrence in uniovular twins suggests an inherited abnormality. The fact that we are continuing to find fast foetal haemoglobin in about 10% of babies born in hospital suggests a similar incidence among all infants born locally. Similar fast-moving haemoglobin components have been reported in isolated cases by other workers. Fessas and Papaspyrou (1957) reported a fast-moving haemoglobin in a Greek infant. It was associated with thalassaemia. Its concentration fell with that of foetal haemoglobin and had almost disappeared at four months. It was not present in the parents. Ager and Lehmann (1958) reported a different fast-moving haemoglobin in a 4-weeks-old infant, and Vella (1959) observed the first haemoglobin in 63 out of 1,962 Chinese cord bloods in Singapore, and the second-haemoglobin " Bart's " in two.

After this investigation was concluded we sent three cord haemoglobins containing fast components to Dr. H. Lehmann, who kindly examined them with the help of Dr. J. A. M. Ager. One—No. 40-A—contained a haemoglobin with the electrophoretic and chromatographic properties of the abnormal foetal haemoglobin " Bart's." The two others—38-A and 44-A—were thought to contain the less well defined haemoglobin described by Fessas and Papaspyrou (1957). On electrophoresis as alkaline *p*H the fast component moved more slowly than " Bart's," and on chromatography at *p*H 6, where " Bart's " is eluted before H, the abnormal bands were seen to move behind H and in front of F.

It is tempting to postulate that our findings indicate hitherto unsuspected abnormal genes occurring in high frequency locally, but we have insufficient evidence at present to justify such speculation. A more detailed investigation of these cases is in progress, the results of which will be published later. It is of interest that Dr. Lehmann informed us that some time ago he had seen haemoglobin " Bart's " in the blood of a negro infant sent to him by Dr. R. Schneider from Galveston, Texas, U.S.A.

Summary

Results of sickling tests, foetal haemoglobin estimations, and paper electrophoresis of the haemoglobin in Nigerian infants at birth and during the first five months of life are presented.

" Fast " haemoglobin fractions were found at birth in 11 of 100 cases studied, and persisted for the first two months of life. Three of these were examined in detail and were found to resemble haemoglobin " Bart's " in one case and the haemoglobin of Fessas and Papaspyrou in two.

Our results are compared with those of other workers and their significance is briefly discussed.

We thank Dr. W. R. F. Collis for permission to undertake this investigation, Professor A. Brown and Dr. J. C. Edozien for use of certain laboratory facilities not available in our department, Dr. J. B. Lawson and the staff of the obstetrics department for supplying samples of cord blood, Dr. O. Ransome-Kuti for assistance with the follow-up, and Dr. C. Adi for technical assistance. We are grateful to Dr. H. Lehmann, of St. Bartholomew's Hospital, London, and to Dr. J. A. M. Ager, of St. Thomas's Hospital, London, for examining three of the " fast-moving " cord haemoglobins.

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INCIDENCE OF DIABETES MELLITUS IN THE BUTHA-BUTHE DISTRICT OF BASUTOLAND

BY

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It has been suggested that the prevalence of diabetes mellitus is low in the Bantu (Trowell *et al.*, 1954; Walker and Bersohn, 1957, 1958; Bersohn and Oelofse, 1957). So far as is known there are no figures to support or controvert this contention. Keeley (1957) has mentioned a total of 153 diabetics out of 37,786 admissions to Baragwanath Hospital during 1956 as contradicting this assertion. However, even Keeley's figures show an incidence of only 0.4%, in contrast to those of Wilkerson and Krall (1947, 1953), who in a typical New England town of the United States of America reported an incidence of 1.7%.

The migration of many Bantu to the urban areas of the Union of South Africa has resulted in a change in their way of life from the primitive to the semi-European. As a result of the change in environmental conditions there is the possibility that ultimately the incidence of certain diseases in the Bantu may be altered. Diabetes mellitus is one of those which may be so affected. Boulay (1928) has pointed to the marked rarity of the disease in French West Africa, where he found it pertinent to publish one case of diabetes mellitus discovered there, and mentions the fact that Nogue and Lhuerre had been unable to find a single case after several years' search both in the Native Hospital at Dakar and among the out-patients at the Institute for Social Hygiene.

On the other hand, American authors (Altschul and Nathan, 1942; Cameron, 1943) have found the American Negro to be just as susceptible to diabetes as the White. Joslin *et al.* (1952) notes that "Negroes appeared at one time to be almost immune to diabetes, but the falsity of this concept has long since been evident from clinical and mortality data." In recent years the Metropolitan Life Insurance Company found that the death rate in Negro males was only about 10% less than that of White males, and was actually 10% higher in the case of the Negro females. DeZoysa (1951) has observed the milder clinical pattern of diabetes in Ceylon as compared with that in the Western world, and attributes it to the high-carbohydrate and low-fat diet consumed in that country.

It therefore becomes necessary to study the incidence of diabetes mellitus in communities where the original primitive conditions prevail and where the food habits and way of life have not yet been affected to any extent by European influence. The object of this paper is to study the incidence of diabetes mellitus in such a community.

Subjects and Methods

The area in which this investigation was carried out is one in which the diet is limited in both quantity and variety. Maize and kaffir corn (in the form of beer and porridge) and vegetables such as wild spinach, pumpkins, peas, and beans are the main items. Meat and eggs are rarely eaten, and milk is obtainable in small quantities during the winter months only.

The body-build of the population varies, most being tall and thin, but a few are obese, particularly older females. Most of the able-bodied males are away working in the mines or are industrial workers, so that the resident population contains a marked preponderance of females.

Three thousand out-patients attending Seboche Hospital were screened for the incidence of glycosuria. All out-patients were accepted for investigation. There were no known diabetics among them. The age of the patients varied from 20 to 85 years (average 36.8 years).

Table I gives an analysis of the age-groups in years involved in this study.

TABLE I.—*Age Incidence of 3,000 Basuto Investigated*

Sex	Age in Years							Total
	20	21–30	31–40	41–50	51–60	61–70	71+	
Males	15	152	156	156	118	55	21	673
Females	158	933	499	316	244	112	65	2,327

The reasons for their presenting at hospital were, in order of frequency, as follows: gastro-enteritis and other diseases of the gastro-intestinal tract, complaints in association with pregnancy, rheumatic conditions, skin eruptions, bronchitis, pellagra, allergies, pneumonia, accidents, heart disease, gonorrhoea, and other urogenital conditions, and florid syphilitic lesions. Some were healthy individuals accompanying patients.

Urines were passed postprandially in the presence of the examiner, who then tested each specimen for the presence of glucose with "tes-tape." All the tests were carried out by the same investigator. The tes-tape was held with a pair of forceps to prevent contamination. It was dipped into the urine and held in the air for one minute. The result was then read. The presence of glycosuria, as shown by a change in colour from the normal yellow to different tints of green and blue, indicated the necessity for a blood-glucose estimation. Venous blood was collected in a tube containing sodium fluoride and thymol to prevent glycolysis, and was dispatched to the South African Institute for Medical Research, Johannesburg. Blood-sugar estimations were carried out by a modified Folin–Wu method (King and Garner, 1947) which measures the true blood glucose—in contrast to the original Folin–Wu method, which measures blood glucose plus saccharoids.

Results

Twelve patients (three males and nine females) showed glycosuria. Table II gives an analysis of the blood-glucose determinations at the time glycosuria was discovered. It will be noted that seven of these cases had blood-glucose levels over 140 mg./100 ml. None of these had symptoms referable to a diabetic state. In fact, the main reasons for attendance were three for tooth extraction, one for constipation, one for congestive cardiac failure, one for pyoderma, and one accompanying a patient.

The ages in this hyperglycaemic group ranged from 30 to 80 years (average 50.6 years). Of these, six were above the age of 40. The total number of out-patients

examined below the age of 40 was 1,913 (323 males and 1,590 females), while above that age there were 1,087 (350 males and 737 females). Thus the incidence of hyperglycaemia in the under-40 age-group was 0.05%, whereas in the above-40 age-group this had increased to 0.55%.

TABLE II.—*Analysis of Patients Showing Glycosuria*

Case No.	Sex	Age in Years	Blood Glucose (mg./100 ml.)
1	F	65	368
2	F	42	254
3	F	30	200
4	M	42	177
5	M	80	165
6	F	45	163
7	F	50	144
8	F	37	132
9	F	45	101
10	F	35	94
11	M	55	81
12	F	33	75

Discussion

This study was carried out on a primitive out-patient community who resent investigation and demand that only immediate illness be attended to. For this reason, a quick easy method of urine examination and as few blood tests as possible were essential requirements for this study. In view of the rapidity of its action tes-tape was thought to be a simple and ideal method of urine investigation. While its value as a quantitative test for glucose has been questioned its value as a qualitative test has been widely accepted (Moran *et al.*, 1957; Jablokow *et al.*, 1957; Leonards, 1957). It has been shown that tes-tape is more sensitive in discovering glycosuria than is Benedict's or a commercial copper-sulphate test (Moran *et al.*, 1957; Chertack and Sherrick, 1959). The latter workers found the results of urine-testing with this procedure to be comparable to those obtained in more elaborate surveys where blood-glucose levels were utilized as the screening procedure.

One possible inaccuracy is that glycosuria may not be apparent where blood-glucose levels are below 175 mg./100 ml. As a result a number of cases could be missed in the absence of glycosuria and the omission of blood-glucose estimations. The figures of Wilkerson and Krall (1947) are of value in this respect. In their survey of 3,516 people they showed that only 8 instances of diabetes were discovered among cases showing initial hyperglycaemia without glycosuria. They consider a venous blood-sugar level over 160 mg./100 ml. as abnormal. The American Diabetes Association (1950), however, has adopted a figure in excess of 150 mg./100 ml. as indicating abnormality. An investigation of the glucose-tolerance test in the healthy Bantu (Politzer, 1955) revealed that the peak level was never higher than 143 mg./100 ml. Lukens (1944) regarded 140 mg./100 ml. as the upper limit of normal. In the present investigation it was decided that this latter level should be adopted as the upper limit of normal, and by this criterion it was found that 7 out of 3,000 cases (0.23%) were diabetic.

Survey findings of Wilkerson and Krall (1947, 1953) in the United States of America indicate that the incidence of diabetes mellitus is 1.7% of the population —that is, 51 diabetics would be expected in a population of 3,000. Our figures indicate a very low incidence of diabetes among the Basuto population analysed. As has been indicated above, it is possible that certain cases might have been missed as a result of blood-glucose estimations having been limited to those cases showing glycosuria. If a similar incidence of hyperglycaemia *sine* glycosuria manifested itself in our Basuto population, as was shown in the Wilkerson and Krall survey, seven further cases would have been found in our present investigation. This would have brought the case total to 14—that is, 0.47% of the population tested. Even this figure must be regarded as a very low incidence, and this in spite of our investigation being carried out on a series of out-patients among whom the incidence might be expected to be higher than that in the general population.

The reason for the variable incidence of diabetes mellitus is not known, but it is of interest to note the few cases reported among the population of French West Africa compared with the high incidence in the Negroes of the United States of America. The difference in the mode of life, particularly food habits, may be important in this connexion. In our present investigation the population analysed live in primitive conditions on a low-calorie diet consisting mainly of carbohydrates. The effects of a low-calorie, low-fat diet were strikingly apparent during the war years, when Himsworth (1949) in Great Britain and Abramson (1947) in Sweden were able to demonstrate a marked reduction in the death rate from diabetes. Similarly, Brauss (1953) has stated that in Germany during both world wars the incidence of diabetes dropped considerably as a result of the reduced food intake. Himsworth (1935a, 1935b, 1936) and Himsworth and Marshall (1935) think that the high proportion of fat in the diet rather than carbohydrate favours the development of diabetes.

The strong possibility exists, therefore, that with the changing conditions of life in the rural areas themselves and with the shift of large portions of these populations to urban areas, there may gradually become evident an increase in the incidence of diabetes among these people. The present investigation highlights the necessity for further studies of a similar nature among primitive communities for comparison with similar undertakings among communities of more advanced status. Only in this way will it be possible to assess the importance of diet and living conditions on the incidence of diabetes mellitus.

Summary

In an examination of 3,000 Basuto in the Butha-Buthe area 12 cases of glycosuria were discovered.

Seven of these cases were found to have blood-glucose levels above 140 mg./100 ml.—that is, 0.23% of the cases examined.

This figure is discussed in the light of a similar investigation in the United States of America, and points to a low incidence of diabetes mellitus in a primitive community.

Stress is laid on the necessity for further studies among similar racial groups living under primitive and under more advanced conditions.

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NITROGEN MUSTARD IN THE PALLIATION OF LUNG CANCER

BY

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Nitrogen mustard (methyl bis(β-chloroethyl)amine), or HN2, has been in use clinically since 1943. Either mustard or its derivatives have been used in the treatment of a variety of malignant diseases. Of these, bronchial carcinoma would seem to be a growth that by virtue of its anatomical site in the lungs would be susceptible to an intravenous cytotoxic agent. Unfortunately the neoplasm does not derive its arterial supply from the pulmonary arteries, but from the bronchial arteries. This means that an intravenous dose of HN2 does not in fact truly perfuse the growth until it has been diluted in the systemic circulation. Nevertheless, the mustard reaching the lung via the pulmonary arteries may be said to bathe the tumour, if only for a very short time.

While all agree that mustard is never curative, there is evidence that a fair proportion of patients do in fact get some alleviation of distress. Thus, Hatch, Bradford, and Ochsner (1956) found in their series of 198 patients that improvement occurred in 46% and that symptomatic relief resulted in more than half the group.

Lynch, Ware, and Gaensler (1950) described the response to HN2 in relation to the histology of the growth: 83% of anaplastic growths, 50% of squamous carcinoma, and 33% of adenocarcinoma were improved.

In a disease problem of the magnitude of lung cancer, which is reaching epidemic proportions, any agent which will produce symptomatic relief in such percentages of patients is worthy of consideration. It is because of the discrepancy between published results and the reluctance of clinicians to use nitrogen mustard that the present series is described.

Present Series

Twenty-five patients were treated with HN2 at three hospitals during the period of 1955–9. All the patients had been rejected for surgery and were also considered unsuitable for radiotherapy. In a sense, therefore, these patients are a selected series in that they were all "poor-risk" cases with advanced disease.

Because of the evil reputation attached to nitrogen mustard for causing many unpleasant side-effects a standard regime was devised to minimize these. Nausea and vomiting are the most constant, and because of this the mustard was always given at night after a light evening meal. The drug was given as an intravenous injection into the rubber of a running normal saline drip. The drip was run very fast for one minute, immediately after the injection, in order to flush the mustard out of the vein. It was allowed to run normally for a further 10 minutes and then taken down.

Two hours prior to treatment sodium amylobarbitone, 3 gr. (0.2 g.), was given and this was repeated one hour before, and again at the time of the injection. If the patient awoke during the night a further 3 gr. (0.2 g.) was given. This 9-gr. (0.6-g.) dose of sodium amylobarbitone was usually adequate to ensure deep sleep until next morning. Occasionally, patients required 12 gr. (0.8 g.), especially if they had been taking barbiturates regularly before admission to hospital.

I have used a number of different drugs, including chlorpromazine, opiates, and cortisone, to determine whether alone or in combination they would prove superior to sodium amylobarbitone. They have not done so, and morphine is particularly noteworthy for its tendency to provoke nausea and vomiting when given after nitrogen mustard.

Initially a dose of 0.1 mg./kg. body weight was given on four successive nights. However, this regime was soon abandoned for a single treatment using 0.4 mg./kg. Quadrupling the dose did not make any significant change in the side-effects observed, and patients appreciated one infusion in place of the four. The patients were admitted for one night, and were then followed in the out-patient department. The treatment was repeated every eighth week.

Malignant pleural effusions resulting from bronchial carcinoma have been treated with local instillations of mustard into the pleural cavity. The procedure is a modification of Weisberger's (1958) method. The effusion is aspirated as completely as possible, and a standard dose of 15 mg. of HN2 diluted in 100 ml. of normal saline is instilled. This is sometimes painful, and, because of this, pethidine, 100 mg. intramuscularly, may be given half an hour before the procedure.

A reactionary effusion may form within 48 hours, and, though it usually reabsorbs, if large, requires aspiration. If fluid is still re-forming, the whole procedure is repeated after one week. Because little HN2 gets out into the general circulation after an intrapleural injection, the dose may be repeated at weekly intervals, or in combination with intravenous mustard without fear of producing bone-marrow depression.

The ages of the 25 patients (4 women and 21 men) ranged between 52 and 72 years (see Table). All were seen as in-patients, and after physical examination had standard chest *x*-ray films taken. Wherever possible, bronchoscopy was performed and a biopsy of the growth taken.

The 25 patients reported here came from a larger group, some of whom have been excluded because an exact histological diagnosis could not be made.

Results

The results have been assessed by the objective clinical improvement, changes in the *x*-ray films, and by the subjective relief of pain and dyspnoea. If before treatment a patient needed large doses of analgesics and afterwards needed little or none, this must count as improvement, even though the *x*-ray films remained unchanged.

Of the 25 patients, 17 (68%) were improved. The cytology seems to influence the response to mustard. Of the 17 benefited by HN2, 11 had anaplastic growths. The remaining six cases comprised squamous-cell carcinoma, adenocarcinoma, and alveolar-cell carcinoma. Apart from the anaplastic group, who are usually mustard-sensitive, there seems little point in further differentiating the neoplasms cytologically. Of the cases responding well to mustard, 66% were anaplastic carcinomata; the remaining 34% constituted all other forms of growth.

Case No.	Age and Sex	Condition Before Mustard	Total Dose and No. of Courses	Response
1	M 56	Collapse of R.L.L.	28 mg. I.V. 1 course	Re-expansion of R.L.L. Died of metastases after 3 months
2	F 69	Right pleural effusion. Mediastinal obstruction (Fig. 4)	5 mg. into pleura. 1 course D.X.T. to mediastinum	Well, with no effusion, 4 months after HN2. (Fluid uninfluenced by D.X.T.) (Fig. 5)
3	M 71	Massive left effusion. Mediastinal mass	22 mg. I.V. 1 course	Died 10 days after treatment
4	M 54	Collapsed L.L.L. with effusion	30 mg. I.P. 2 courses	Pain-free with no effusion 8 months after HN2
5	M 68	Collapsed L.U.L.	46 mg. I.V. 2 courses	Well after 6 months. No re-expansion of L.U.L.
6	M 52	Left pleural effusion. Mass in R.U.L.	42 mg. I.V. 2 courses	Chest pain relieved, but died 4 months after HN2
7	M 55	Bony metastases. Mass in L. main bronchus	25 mg. I.V. 1 course	Bone pain relieved. Died 1 month after HN2
8	M 66	Haemoptysis +++. Collapsed R.U.L.	100 mg. I.V. 4 courses	Haemoptysis dramatically eased. Clearing in R.U.L. Died 10 months after first course
9	M 66	Collapsed R.M.L. and R.L.L. with effusion (Fig. 1)	69 mg. I.V. 3 courses	Effusion cleared. Died after 7 months with carcinomatosis (Fig. 2)
10	M 58	Pul. tub. and neoplasm. Collapsed L.U.L. Bony metastases	48 mg. I.V. 2 courses	Bone pain greatly diminished. Died 3 months after HN2
11	M 64	Collapsed R.U.L. S.V.C. obstruction	46 mg. I.V. 2 courses	R.U.L. re-expanded. Jugular venous pulse lowered. Died 9 weeks after HN2
12	M 70	Collapsed L.L.L.	24 mg. I.V. 1 course	No response. Died 2 months later
13	M 53	S.V.C. obstruction	48 mg. I.V. 2 courses	J.V.P. lowered. But recurred after 5 weeks. Died
14	M 53	Collapsed R.U.L. Chest pain +++	66 mg. I.V. 3 courses	Partial re-expansion of R.U.L. Pain less. Died 6 months after HN2
15	M 72	Right pleural effusion	48 mg. I.V. 30 mg. I.P. 2 courses each	Effusion absorbed. Lung unchanged. Died 8 months after HN2
16	F 68	S.V.C. obstruction	60 mg. I.V. 2 courses	Dramatic response initially, but died 4 months after first course
17	M 70	L. phrenic paralysis. Mass at left hilum	75 mg. I.V. 3 courses	No change. Died 6 months after HN2
18	F 67	Lymphangitis carcinomatosa	25 mg. I.V. 1 course	No change. Died 3 weeks later
19	M 62	Right pleural effusion N.G. R. main bronchus	45 mg. I.P. 3 courses	Effusion cleared. Died of metastases 4 months after HN2
20	M 66	Collapsed R.M.L. and R.L.L.	46 mg. I.V. 2 courses	Less dyspnoeic. Died 3 months after HN2
21	M 72	Total collapse of L.U.L.	28 mg. I.V. 1 course	No change. Died 6 weeks later
22	M 63	Recurrent laryngeal and L. phrenic paralysis	30 mg. I.V. 1 course	No change. Died 3 weeks later
23	M 60	Mediastinal obstruction. Right effusion	32 mg. I.V. 15 mg. I.P. 1 course	Partial clearing of effusion. Died 8 weeks after HN2
24	M 58	Hemiplegia. Pneumonectomy 18/12 before	28 mg. I.V. 1 course	Bone pain dramatically improved. Died 1 month after HN2
25	F 64	"Alveolar-cell" carcinoma	69 mg. I.V. 3 courses	Less dyspnoea but x-ray unchanged. Alive 6 months after HN2

The survival time of the group is poor, the longest survival after treatment being 10 months (Fig. 1). The patient with the alveolar-cell carcinoma is probably alive only by virtue of the slow progression of this neoplasm. It is emphasized that HN2 does not prolong life in these patients, and is given purely as a palliative measure.

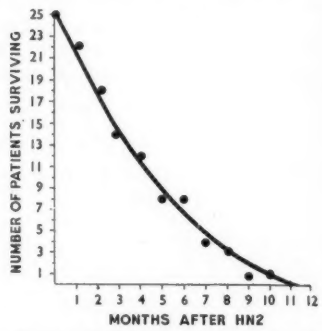

FIG. 1.—Survival time in months of 25 cases of lung cancer treated with nitrogen mustard.

Side-effects.—These may be divided into two groups—the immediate and the delayed. Of the former, local thrombophlebitis at the injection site, headache, nausea and vomiting, and diarrhoea have been described. For practical purposes only nausea and vomiting are of any importance. By using the regime outlined, these unpleasant symptoms can be reduced to a minimum. Of the 25 patients, 12 awoke in the night, usually about four hours after the injection of HN2, and vomited once. They could not remember the experience the day after. Just over half the group slept uneventfully and awoke the next day without experiencing any unpleasant symptoms. This is such a common experience that it is difficult to appreciate the reluctance of many clinicians to use mustard on account of its "great toxicity." The delayed side-effects

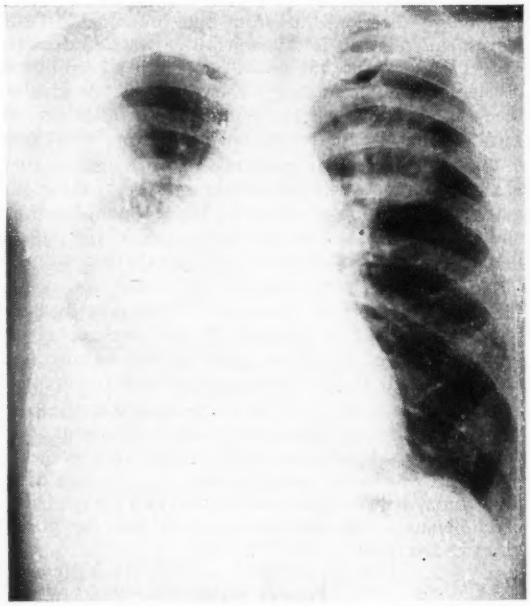

FIG. 2.—Case 9. Right pleural effusion with collapse-consolidation of right middle and lower lobes, before treatment with intravenous nitrogen mustard.

of HN2 are related to its activity as a depressant of bone-marrow activity. If the total white-cell count in the peripheral blood is below 5,000 cells per c.mm. the drug is withheld. Blood counts have been taken at regular weekly intervals after treatment, but no significant leucopenia has been found.

Discussion

The present results agree well with the experiences of Lynch *et al.* (1950). These authors studied 60 patients, and used dosages of mustard varying from 0.1 to 3 mg./kg. They gave the mustard until depression of the leucocyte count in the peripheral blood was engendered. They advise continuing the drug until the percentage of lymphocytes in the circulating blood begins to fall. They maintain that certain patients show regression of the neoplasm only when this stage of lymphopenia is induced. To minimize nausea and vomiting, 100 mg. of pentobarbitone was given. This is a small dose as compared with the sodium amylobarbitone which I usually give. Nevertheless, 17 of the patients of Lynch *et al.* had no nausea or vomiting. They found that the anaplastic growths were the most mustard-sensitive (83% improved); only 50% of squamous-cell neoplasms and 33% of adenocarcinoma responded. This sensitivity of anaplastic growths to HN2 is a constant finding.

Kent and Reh (1950), in a series of 19 cases of lung cancer, found that the anaplastic growths responded best to mustard. Levine and Weisberger (1955) went further, and stated that, of the anaplastic carcinomata, only the "small-cell carcinoma" is truly mustard-sensitive. They claim that HN2 has no significant effect on squamous-cell carcinoma, adenocarcinoma, or "anaplastic" carcinoma. For this reason they split off the "small-cell carcinoma" as a distinct entity away from the anaplastic group. They gave doses of HN2 varying from 0.4 to 1.5 mg./kg., but no benefit was observed in increasing the dose above 0.4 mg./kg.

Hatch *et al.* (1956), in their study of 198 patients, summed up their results when they stated that there was good subjective improvement but no prolongation of life. 46% of this group were improved by HN2.

The present series of 25 patients fits into the pattern observed by previous authors (see above). HN2 does not prolong life in patients suffering from carcinoma of the bronchus; neither does it compete with thoracic surgery or radiotherapy as the elective treatment for such cases. What does emerge after 16 years' collective experience is that HN2 has a useful, albeit limited, role in the management of lung cancer. It is essentially

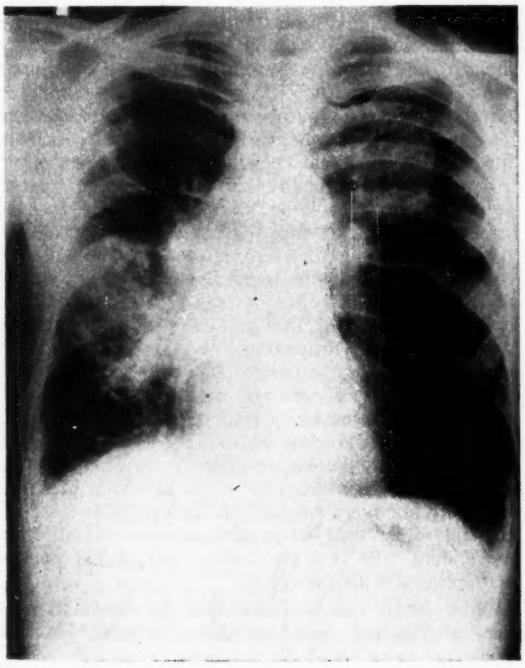

FIG. 3.—Case 9. After nitrogen mustard. The right side shows clearing of the effusion and re-expansion of the collapsed lobes. The lesion in the left upper lobe is unchanged.

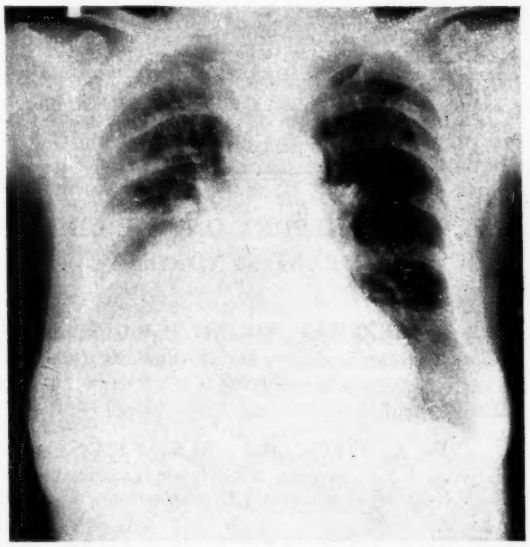

FIG. 4.—Case 2. Malignant right pleural effusion which persisted despite deep *x*-ray therapy to the mediastinum.

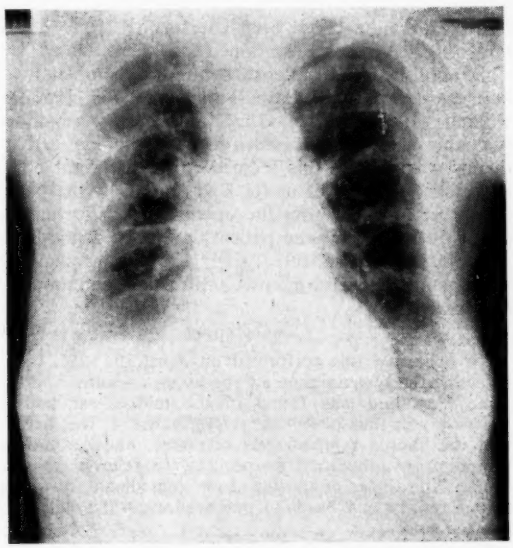

FIG. 5.—Case 2. After 5 mg. of nitrogen mustard intrapleurally. The effusion did not recur.

palliative, but any therapy capable of affording symptomatic relief to over two-thirds of otherwise untreatable patients should not remain neglected.

Summary

25 patients with advanced lung cancer were treated with HN2. The results are described, and some correlation with the tumour cytology is made.

A regime for minimizing the side-effects of HN2 is described in detail.

The literature is briefly reviewed.

It is a pleasure to thank Drs. James Blake, Michael Ashby, Peter Davies, Donald Hunter, and Kenneth Perry for their encouragement during this study.

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A FURTHER REPORT ON THE CHORDA TYMPANI SYNDROME

BY

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In an article on unilateral sweating of the submental region after eating, including a case report, it was suggested that the symptom-complex be termed "the chorda tympani syndrome" (Young, 1956).

An operation has been performed, the chorda tympani nerve being sectioned on the affected side. This abolished the patient's symptoms completely for one year and partially for still longer. Bauer (1956) and Roland (1956) advocated sectioning of the chorda tympani nerve as it crossed the middle ear. If the theory was correct this seemed to be the right course to pursue, and one of us (G. E. S.) then saw the patient and agreed to carry out the operation. Unfortunately, about the same time the patient developed a middle-ear infection on the affected side, so nothing could be attempted for several months, until all the inflammation had abated.

Case Report

An operation was performed on April 29, 1957, but on reflecting the tympanic membrane by an endaural approach some free fluid was found in the middle ear and the anatomy was thus obscured. Nevertheless, it was believed that the chorda tympani was sectioned, and certainly all symptoms of abnormal sweating were relieved at once. Eating an apple or tasting sour ingredients no longer caused redness and beads of perspiration on the chin of the affected side.

It was decided to publish the result of the operation, but six months later symptoms began to recur. It was thought that the nerve had regenerated, and it was deemed wise to repeat the operation, but, this time, to remove a portion of the nerve rather than just section it.

This was carried out (G. E. S.) on May 13, 1958. For almost a year after that the patient was completely free of her embarrassing symptoms and was delighted with the result.

However, on questioning and examining her on May 19, 1959, she stated that at breakfast-time one morning early that month she had again sustained a flushing of the right side of the face and a little sweating. She had not taken any unusual or stimulating food that morning. After trying out one or two tests with negative results it was decided to reassess her condition at a later date.

The next examination took place on October 8, 1959. The patient stated that since the first recurrence of trouble early in May she had had several recurrences of flushing and sweating, but all except one had occurred at breakfast-time, the exception being at lunch-time. The attacks occur about one to three times a week, but are not nearly so severe as they used to be and really cause very little trouble or embarrassment. They do not appear to be associated with any particular food. Curiously enough, she seems to know when the attack is likely to occur, because on the days concerned she is conscious of a flow of saliva into the mouth on getting up in the morning and before taking her breakfast. She has had no trouble later in the day (except on the one occasion at mid-day) or when having a meal away from home—for instance, if she goes out in the evening on a social occasion.

When given a sour apple to eat (May 19, 1959, and again on October 8) no reaction occurred. The skin of the chin and face did not show signs of flushing or sweating as it did pre-operatively. There is no loss of taste sensation on eating. Hearing is only very slightly diminished in the right ear (she can still hear a watch ticking), but this may not be due to the operation, because, as noted above, she suffered from middle-ear inflammation before the attempts were made to sever the chorda tympani nerve.

Discussion

The original case report and the discussion regarding causation of the condition excited a great deal of interest, and letters were received from many places, some as far away as Vancouver, Capetown, and Czechoslovakia. A number of letters and articles have also appeared in the *British Medical Journal* discussing the cause of abnormal sweating of the face, particularly in regard to the auriculo-temporal syndrome. It would seem that in these cases, whether they be auriculo-temporal or chorda tympani syndromes, abnormal nerve regeneration is regarded as being the explanation of the conditions, though the mechanism of the abnormal regeneration is still not clear. Whatever the actual cause, sectioning of the particular nerves concerned seems to be a rational procedure. Unfortunately, whether it be the auriculo-temporal nerve which is concerned or the chorda tympani as in the above case, regeneration seems likely. In this case, however, the recurrence of mild symptoms after one year is interesting in that they no longer seem to be brought on by sour or bitter ingredients but occur mostly at breakfast-time, and not every day, suggesting a possible emotional element rather than an anatomical one. At all events the patient, who is a fine-looking girl of 17½ years, is very pleased with the result.

No evidence can be found that the chorda tympani has ever before been sectioned in order to treat unilateral sweating of the submental region.

This particular case report would seem to show that the chorda tympani syndrome is a definite entity which

can be relieved at least temporarily, without any disfiguring scar, by section of the relative chorda tympani nerve as it crosses the tympanic membrane.

It remains to be seen whether over the years the syndrome will again establish itself as a definite entity as before the operation, which would imply a regeneration of the nerve.

We thank Mr. Francis Bauer and Mr. P. E. Roland for their advice, which led to the attempted operations for relief of the condition.

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Medical Memoranda

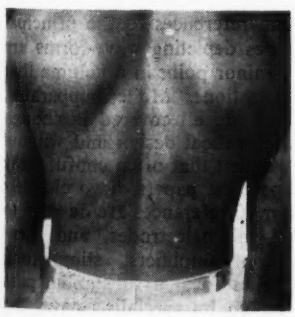
Hypermelanotic Rash Associated with Sulphonamide Therapy

The various skin rashes associated with sulphonamide therapy, in the production of which idiosyncrasy, allergy, and photosensitization may play a part, are well recognized (Smith, 1944 ; Freeman, 1944 ; Lawrence and Francis, 1953).

In the course of an investigation into the occurrence of a hypermelanotic macular eruption during dapsone treatment for leprosy among deeply pigmented Bantu patients in the Belgian Congo (Browne, 1959a, 1959b, 1959c)—an eruption differing from the drug-dermatitis already reported (Lowe, 1950 ; Barnes and Barnes, 1951 ; Allday and Barnes, 1951)—two cases were observed in which an identical eruption was apparently caused by sulphaguanidine and sulphathiazole.

CASE 1

A Congolese medical assistant suspected that his wife had on several occasions put poison in his food, occasioning bouts of diarrhoea and recurring crops of hypermelanotic macules ; he therefore instituted proceedings for divorce. Circumspect inquiry revealed that his suspicions were first aroused by the rash, and not so much by the diarrhoea ; and further questioning elicited the information that the rash appeared for the first time after he had treated the diarrhoea with sulphaguanidine, a total dose of 20 g. spread over three days. On the last day of this treatment he experienced widespread irritation, and many small bullae appeared on the skin, which, after being scratched, left a raw bleeding surface. Within a few days the bullae healed, but the skin in those areas was black in colour.



Photograph of Case 1, showing rash on back.

During the following months he suffered from several attacks of diarrhoea ; and each attack, treated by himself (in an isolated bush dispensary) in the same way, was followed by the same sequence : pruritus, bullae formation, hyperpigmented macules.

He had never seen such an eruption before, and jumped to the diagnosis that was, to him, the likeliest, explaining both the rash and the diarrhoea.

During the next 12 months, he had no further attacks of diarrhoea, and the macules slowly faded and almost disappeared. Conjugal harmony was restored. Then a single attack of diarrhoea, treated with 7 g. of sulphaguanidine in one day, was followed by the same sequence, and the same suspicions of his wife's murderous intentions. I saw him a few days afterwards, and took the accompanying photograph. Fortified by my personal observations in the matter of dapsone therapy, I was able to suggest the true explanation of the rash (and convince him of it) and offer counsel.

CASE 2

A Bantu woman aged 22 was given oral sulphathiazole for a pustular dermatitis of the forearms ; she received 2 g. daily for three days. A week later a hyperpigmented rash appeared, first on the forearms, then on the face, trunk, and legs, but without previous bulla formation. The skin over the whole body irritated intensely. The appearance of the individual elements and the disposition of the rash were similar in all respects to the case recorded above, after the healing of the bullae.

The macules gradually faded, but were still visible six months later as vague blackish spots in the skin.

COMMENT

Neither patient at the time of the examination showed toxic signs attributable to the treatment undergone, and no history of such signs could be obtained. The urine was normal to the usual chemical and microscopical tests.

In both cases the elements of the macular eruption were widely distributed over trunk, limbs, and face, sparing the hairy scalp and the extremities. They were black or, in some lights, dark purplish black, set in a dark-brown skin.

Histological examination of similar macules associated with dapsone therapy reveals masses of a melanin-like pigment deposited in the superficial layers of the corium, both in melanophores and free. The melanocytes are apparently normal.

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The teaching programme of the University of Pittsburgh School of Medicine will be strengthened this year as a result of a $400,000 gift from the A. W. Mellon Educational and Charitable Trust. Funds from the gift will be used over an eight-year period to expand the teaching programme of the school's Department of Preventive Medicine from July 1.

Reviews

MERCER'S ORTHOPAEDICS

Orthopaedic Surgery. By Sir Walter Mercer, M.B., Ch.B. (Edin.), M.Ch.Orth.(Liv.)(Hon.), F.R.C.S.(Edin.), F.A.C.S. (Hon.), F.R.C.S.(Eng.)(Hon.), F.C.S.So.Af.(Hon.), F.R.C.S.I. (Hon.), F.R.S.(Edin.). Fifth edition. (Pp. 1,075+xi; illustrated. 90s.) London: Edward Arnold (Publishers) Ltd. 1959.

Mercer's *Orthopaedics* was first published twenty-seven years ago and the fifth edition is most welcome. The reader will find ideal descriptions of all that is best in British orthopaedic surgery written by one of the leading surgeons of the day. The value of inviting the help of colleagues at the Edinburgh Medical School is shown by their contributions on particular subjects, which include hand infections (John Bruce), bone tumours (Eric Mekie), and spastic paralysis (George Pollock). This is a comprehensive book which includes a chapter on circulatory disturbances of the extremities. Although few orthopaedic surgeons may treat such conditions, it will be useful to them as well as to other surgeons who use this book.

There has been a thorough revision, and it will be found that general affections of the skeleton, congenital conditions, scoliosis, and the paralyses are among the subjects which have been entirely rewritten. The principles of diagnosis and treatment are well described, particularly of anterior poliomyelitis and spastic paralysis, torticollis, Volkmann's ischaemic contracture, and causalgia. There is a useful section on "Some Complications of Trauma"—the treatment of un-united carpal scaphoid being excluded—and on affections of soft tissues. Silk is still advocated for suture of ruptured tendo achillis, but reasons for its use are not stated. It is clear that the author considers that the work of Smith-Petersen and Judet has not solved the difficulties of hip surgery in connexion with fracture and osteo-arthritis, as he describes a number of treatments, all of which may be ineffective, but each method has its own supporters. The chapters on syphilis of bone and tuberculosis of bones and joints are excellent and should be useful to those working in countries where these conditions are still prevalent. The subject-matter throughout is of high standard and there are over four hundred useful illustrations, mostly small but explanatory and not ostentatious. There are over a dozen pages of modern bibliography.

The revision of this book is a credit to Sir Walter and to all who helped him, including publisher and printer. It will be invaluable to postgraduates, to those reading for examinations, and particularly to surgeons in the Commonwealth and other parts of the world who wish to maintain the standard of their work at the high level of the teaching schools of Great Britain.

ST. J. D. BUXTON.

MEDICINE'S TRUE REWARD

The Rewards of Medicine, and other Essays. By Hugh Barber. (Pp. 140. 15s.) London: H. K. Lewis and Co., Ltd. 1959.

This well-printed and produced book contains a collection of delightful essays by a humanist-physician. The essay, which gives the book its title, dwells perhaps a little too much on the past and present financial rewards of the profession. "The labourer is worthy of his hire," but the true reward of medicine, as the author intimates with an apt quotation from Marcus Aurelius, is the interest of the work.

Among the more literary essays "The Value of Fiction in Medical Education," "Smollett's Contribution to Medicine," "Erasmus Darwin," and "Jane Austen's Medical Wisdom" are all informative. In the last-named essay Dr. Barber suggests that Jane Austen's last illness may have been pernicious anaemia. Alternatively, there are grounds for the view that she died from pulmonary tuberculosis. If so, hers was a case of contact infection through nursing her brother, Henry, who was seriously ill with this disease in London in 1815. Henry recovered, but in 1816 Jane's health declined and she died in 1817.

The essay on "The Body-snatchers" is a useful sketch of a macabre subject. It may interest Dr. Barber to know that the fate of Hare, who turned King's evidence in the Burke and Hare murders, is not altogether unknown. Sergeant Ballantine, writing in 1882, said that Hare found work in a lime-pit, but his fellow-workers, becoming aware of his identity, threw him into the quicklime, which destroyed his eyesight. Sir John Rose Bradford told me that when a boy in the years 1868–70 he frequently saw a blind beggarman in a white smock led by a woman in London's Oxford Street; his father informed him that this mendicant was Hare. Laymen as well as doctors will enjoy these essays.

ARTHUR S. MACNALTY.

ELECTRONICS IN BIOLOGICAL RESEARCH

Electronic Apparatus for Biological Research. By P. E. K. Donaldson, M.A., with contributions by J. W. L. Beament, M.A., Ph.D., F. W. Campbell, M.A., D. W. Kennard, M.B., B.S., M.R.C.S., L.R.C.P., Ph.D., R. D. Keynes, M.A., Ph.D., K. E. Machin, M.A., Ph.D., A.M.I.E.E., and I. A. Silver, M.A., Ph.D., M.R.C.V.S. (Pp. 718+xii; illustrated. £6.) London: Butterworths Scientific Publications. 1958.

This comprehensive handbook brings together items of theory and practice that have hitherto been scattered throughout a very wide literature, and should be valuable to both experienced electrophysiologists and students. The student who is entering the field of biological research will appreciate the concise way in which the basic theory is presented, and those who require a more specialized treatment of particular theoretical aspects will find references to the principal publications. Several figures depicting wave-forms are badly drawn, but this is a minor point in a volume that contains so many clear illustrations. Modern apparatus, components, and know-how are all covered in enough detail for the purposes of practical design and without the lengthy theoretical treatment that often confuses the non-specialist reader of specialist papers. Two chapters of 50 pages containing over 70 references are devoted to the important subject of microelectrodes, and these together with chapters on amplifiers, stimulators, recorders, and power supplies form a substantial part of the book. Sections written by specialists cover the control and measurement of humidity, temperature, light, and radioactivity in detail that should be adequate for most purposes.

There is one important feature of the book that deserves special mention—namely, the useful set of 34 graphs showing the performance of filters and attenuators. These are collected together, and, though they illustrate points in various chapters, each graph is complete in itself, since the circuit and all parameter values are indicated beside the curves. It is fortunate

that the author was able to include the final stop-press chapter on transistors: this gives a clear picture of their operation and possible uses in biological research.

W. K. TAYLOR.

OCULAR MUSCULAR ANOMALIES

Strabismes, Hétérophories, Paralysies Oculo-motrices. (Les Déséquilibres Oculo-moteurs en Clinique). By René Hugonnier. Preface by Professor Paufique. (Pp. 748+viii; illustrated. 8,500 fr.) Paris: Masson et Cie. 1959.

In the last few decades our understanding of the mechanism of squint and our views regarding the treatment of anomalies of binocular vision have been revolutionized, and it is only fitting that from the country wherein modern views of these anomalies were initiated almost a century ago by Javal and Parinaud a comprehensive textbook should now appear. It is fortunate that this work should have been undertaken in the school of Lyons where René Hugonnier, with the assistance of his talented wife, has for some considerable time been responsible for the clinic dealing with ocular muscular anomalies; and the result has exceeded our expectations.

The importance of this subject is not generally recognized, for, apart from the widespread infective conditions which are a tragically frequent cause of blindness in the underdeveloped regions of the world, these anomalies are the most frequent cause of disabilities of vision. To-day in France the authors estimate that a million people suffer from amblyopia in one eye, and one and half millions from squint—a figure greater than those suffering from cataract, glaucoma, and retinal detachment combined; the same thing probably applies to Great Britain and all Western nations.

In the present volume the entire subject of ocular muscular imbalance, squint both concomitant and paralytic, as well as motor anomalies such as nystagmus, is reviewed in considerable detail—the aetiology and evolution of these anomalies, the methods of investigation of the patient, and treatment by spectacles when applicable, orthoptics, and surgery. The teaching is sound and the views expressed are up to date. The book is worth getting if only to read "aphorisms" at the end. "To become an orthoptist it is not sufficient to procure an orthoptoscope; one cannot play a violin because one buys one." "There is no magic in orthoptic exercises." "The psychological effects of squint affect the parents sometimes more than the children."

STEWART DUKE-ELDER.

TERRIFYING MICROBE

Staphylococcus Pyogenes and its Relation to Disease. By Stephen D. Elek, M.D., D.Sc., Ph.D., D.P.H. (Pp. 767+vi; illustrated. 84s.) Edinburgh, London: E. and S. Livingstone Ltd. 1959.

The golden staphylococcus, cause of the homely boil, has excited the minds of many doctors and scientists since 1880, when it was identified (and named) as a pyogenic coccus by Sir Alexander Ogston, professor of surgery in Aberdeen.

In the past decade the general concern with the staphylococcus as "enemy No. 1" in hospital infection has caused a fresh outburst of investigations into its properties and pathogenicity. It is fortunate for us that one of the chief protagonists in this field, Professor S. D Elek, has been so dedicated as to write a monograph of 767 pages, including 237 pages of bibliography, on this common parasite of man and animals. He prefers, as I do, the name *Staphylococcus pyogenes* to the perhaps taxonomically more correct *Staphylococcus aureus*; for pigment production is a variable factor and the production of coagulase is now generally accepted as the best and simplest criterion of potential pathogenicity. Elek deals in great detail with the morphology, metabolism, and antigenic structure of the staphylococcus, its susceptibility to phage, the nature and function of coagulase, and the wide range of diffusible products and their possible relationship to pathogenicity.

In all these earlier chapters there is evidence of an intimate knowledge of bacteriology and microbial chemistry which will be of most interest and value to the microbiologist and the research worker. The later chapters on infection and immunity, the effects of antiseptics and antibiotics on the staphylococcus, and the clinical problems of staphylococcal infections will appeal to a much wider audience; they give a remarkably balanced picture of present-day knowledge and beliefs.

In reviewing a vast literature the author must try to sift the wheat from the chaff, and this Professor Elek has done quite successfully. At the same time he sometimes expresses his own dogmatic opinion, and his dogmatism may not always find general approval. However, there can be nothing but praise and gratitude to the author for having given us this detailed and up to date picture of a fascinating, and sometimes terrifying, microbe.

ROBERT CRUICKSHANK.

THE PHENOTHIAZINES

Die Phenothiazinderivate in der Medizin. Klinik und Experiment. Edited by Professor H. Kleinsorge, M.D., and Dr. K. Rösner. (Pp. 328; illustrated. DM. 31.60.) Jena: VEB Gustav Fischer Verlag. 1958.

In Great Britain we rarely come across books produced in the Eastern Zone of Germany. This volume on the "Phenothiazine Derivatives in Medicine," written by two physicians from Eastern Germany, is an account of the pharmacology, toxicology, and medical uses of these compounds. The authors recruited the help of a psychiatrist and several surgeons and gynaecologists from Western Germany to cover the therapeutic uses of the phenothiazines in mental disease and surgical practice.

The main part of the book is that written by the physicians, Professor Kleinsorge and Dr. Rösner. It gives a comprehensive and balanced account of present-day knowledge and includes some of the authors' own experimental work. The literature from English-speaking countries is adequately represented, but a large proportion of the references are from Continental countries and culled from both sides of the iron curtain. Thus the British reader is provided with a survey of papers with which he is not likely to be familiar.

In spite of much fundamental work done on the phenothiazines, the understanding we have of the versatile uses of, say, chlorpromazine is very limited and their explanation controversial. The different views are adequately stated by Kleinsorge and Rösner, who also supply detailed instructions for the treatment of individual diseases. Such instructions make up the bulk of the second part of the book, written by surgeons and other specialists. Their recommendations are essentially empirical, based on theories about which there is little agreement among physicians and pharmacologists. It

is interesting to find that, in contrast to the tendency in Britain to use one or few drugs at a time, the French "lytic cocktails" and other combinations are very popular with the authors of this book. The relatively small space devoted to the psychiatric uses of the phenothiazines is in striking contrast to the great interest in this topic shown in the English-speaking countries.

MARTHE VOGT.

EXTRACORPOREAL CIRCULATION

Extracorporeal Circulation. Compiled and edited by Dr. J. Garrott Allen. Assisted by Dr. Francis D. Moore, Dr. Andrew G. Morrow, and Dr. Henry Swan II. (Pp. 518+xxii; illustrated. 57s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

This book contains the papers and discussion at a conference held in Chicago in 1957, attended by representative experts from the Western world. Five years ago this subject was in its infancy, and beset by innumerable doubts and difficulties. The early workers in Great Britain and elsewhere had to endure many setbacks and disappointments, but they are now reaping the reward of their patience and persistence. All who are interested in the detail of the technical problems of the extracorporeal circulation and their solution should read this book. The problems of oxygenators of various types, the prevention of air embolism and of clotting, and the effects of perfusion on various organs such as brain, kidney, and lungs are all discussed. The final chapter contains definitions and an agreed nomenclature formulated by a representative Anglo-American committee. We have come a long way since Sydney Ringer stopped the frog heart with potassium and since the invention of the Dale–Schuster pumps for physiological perfusion, and the leaders of this surgical research deserve our congratulations.

This book has been rushed into print, and it is marred here and there by inadequate proof correction, especially in the informal discussion, and by the absence of an index. It is, however, a mine of valuable information for cardiologists and surgeons involved in these spectacular technical advances, which are creating further immense opportunities for cardiological research.

J. MCMICHAEL.

In 1957 the Josiah Macy Jr. Foundation, of New York, organized a fourth conference at Princeton on "Neuropharmacology." A report of it has now been published (pp. 285; $5) by the Foundation. The topics discussed at the conference included the effects of lysergic acid diethylamide (LSD), the action of mescaline and related compounds, the study of certain cerebral responses in monkeys by the implantation of electrodes, and experiments on human volunteers with a substance called taraxein, a globulin fractionated from the serum of schizophrenic patients. This is a book primarily for specialists in the subject, though the conversational manner in which the Foundation conducts these conferences makes the report less heavy going than a series of papers would be. It has indeed its piquant moments:

"*Hoagland:* Does anybody know of any confirmation of the psychosomimetic effects of either adrenochrome or adrenolutin by any other group?

"*Heath:* No.

"*Mirsky:* No

"*Hoagland:* Is this because it has not been tried by other people?

"*Mirsky:* It's been tried by everybody."

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Physiological Basis of Diuretic Therapy. By Robert F. Pitts, Ph.D., M.D. (Pp. 332+xiv; illustrated. 78s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Biological Problems of Grafting. A Symposium Sponsored by the Commission Administrative du Patrimoine Universitaire de Liège and the Council for International Organizations of Medical Sciences, March 18–21, 1959. Edited by F. Albert and P. B. Medawar. (Pp. 453+xii; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1959.

The Royal College of Surgeons of England. A History. By Zachary Cope, Kt., F.R.C.S. (Pp. 360+xii; illustrated. 63s.) London: Anthony Blond. 1959.

First International Congress of Neurological Sciences, Brussels, July 21-28. Volume V. ***Joint Meetings.*** Edited by L. van Bogaert and J. Radermecker. (Pp. 219; illustrated. 70s.) London, New York, Paris, Los Angeles: Pergamon Press. 1959.

General Anaesthesia. Edited by Frankis T. Evans, M.B., B.S., F.F.A. R.C.S., D.A., and Cecil Gray, M.D., F.F.A. R.C.S., D.A. Volume I: ***Basic Principles.*** Volume II: ***Techniques, Special Fields and Hazards.*** (Pp. Vol. I: 531+29+xi; Vol. II: 431+29+xiii; illustrated. £7 7s. per set.) London: Butterworth and Co. (Publishers) Ltd. 1959.

Cancer. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Volume 6. Part X: ***Chemotherapy.*** Part XI: ***Public Health and Nursing Aspects of Cancer.*** Pp. 500+17+ix; illustrated. 85s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

The Cash-In. By Alan J. Keyes. (Pp. 288. 16s.) London: Hodder and Stoughton. 1960.

Az Orvosi Hetilap Centenáriumi Emlékkönyve. (Pp. 175; illustrated. Ft. 45.) Budapest: Medicina Könyvkiadó. 1959.

British Medical Bulletin. Volume 16, No. 1. ***Antibiotics in Medicine.*** (Pp. 88+xvii; illustrated. 20s.) London: Medical Department, British Council. 1960.

Brucella Infection and Undulant Fever in Man. Sir Weldon Dalrymple-Champneys, Bt., C.B., D.M., D.P.H., F.R.C.P. (Pp. 196+xii; illustrated. 25s.) London, New York, Toronto: Oxford University Press. 1960.

Parasites and Parasitic Infections in Early Medicine and Science. By R. Hoeppli, M.D., D.Sc. (Pp. 526+xiv; illustrated. 63s.) London: Oxford University Press, for Malaya University Press. 1959.

Growth Diagnosis. Selected Methods for Interpreting and Predicting Physical Development from One Year to Maturity. By Leona M. Bayer and Nancy Bayley. (Pp. 241+xiv; illustrated. 80s.) Chicago: University of Chicago Press. London: Cambridge University Press. 1959.

Back View. By Sir Harold Morris, Q.C. (Pp. 244; illustrated. 25s.) London: Peter Davies. 1960.

Cancer of the Breast. Compiled and edited by Willard H. Parsons, M.D., F.A.C.S. (Pp. 232+xv; illustrated. 60s.) Oxford: Blackwell Scientific Publications. 1959.

Infectious Diseases of Animals: Diseases Due to Bacteria. Edited by A. W. Stableforth, D.Sc., M.R.C.V.S., D.V.S.M., and I. A. Galloway, D.Sc., M.R.C.V.S. In two volumes. (Pp. Vol. I: 396+x; Vol. II: 397-810+x; illustrated. £8 per set.) London: Butterworths Scientific Publications. 1959.

The Anatomy of Judgment. An Investigation into the Processes of Perception and Reasoning. By M. L. Johnson Abercrombie, B.Sc., Ph.D. (Pp. 156; illustrated. 25s.) London: Hutchinson and Co. (Publishers) Ltd. 1960.

Chemical Concepts of Psychosis. Proceedings of the Symposium on Chemical Concepts of Psychosis held at the Second International Congress of Psychiatry in Zurich, Switzerland, September 1–7, 1957. Edited by Max Rinkel and Herman C. B. Denber. (Pp. 485+xxi; illustrated. 63s.) London: Peter Owen, Ltd. 1960.

Frontiers in Science. A Survey. Edited by Edward Hutchings, Jr. With editorial commentaries by L. A. DuBridge, George W. Beadle, Harrison Brown, and Hunter Mead. (Pp. 362+vi; illustrated. 25s.) London: George Allen and Unwin, Ltd. 1960.

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MYELOSCLEROSIS

Myelosclerosis, or myelofibrosis, is a syndrome which is being diagnosed with increasing confidence because a distinct clinical picture has become clear and new techniques, especially splenic puncture, are useful in confirming the diagnosis. The syndrome is characterized by a slowly progressive anaemia with leuco-erythroblastosis. The spleen gradually enlarges and eventually becomes gross; fibrous tissue and new cancellous bone infiltrate the bone marrow. When only fibrous tissue is present in the marrow, the name "myelofibrosis" is sometimes used, but it is clear that, with or without cancellous bone, the condition is the same. This syndrome sometimes appears as a terminal stage in some other blood diseases, notably polycythaemia vera and chronic myeloid leukaemia, and some haematologists have followed William Dameshek[1] in classifying them all together as the "myeloproliferative" disorders. But such changes are not very frequent, and there is little doubt that myelosclerosis exists independently.

Notable changes occur in the *x*-ray appearances of the bones in about one-third to one-half of the patients. Thus T. F. Leigh and his colleagues[2] in Atlanta, Georgia, found radiological changes in 11 out of 22 cases for which they had radiographs. They describe the abnormality as a diffuse osteosclerosis; the affected bones are not expanded and there is no change in their external contour; the sclerosis is due to thickening of the individual bone trabeculae and the formation of some new trabeculae in the spongiosa. The ribs, vertebrae, clavicles, scapulae, and the metaphysial ends of the femora and humeri are most frequently affected. Leigh and colleagues comment that the combination of osteosclerosis with splenomegaly almost always means that the diagnosis is myelosclerosis, and, with a radiologist's eye, they say that on routine examination "splenomegaly will usually be suggested by the elevation of the left diaphragmatic leaf." F. Mulcahy[3] examined radiographs of the bones of 19 known cases of myelosclerosis and found that nine showed changes of various degrees, four being abnormal on "casual inspection." He notes that the earliest change is an increased prominence of trabeculation against a background of slightly higher density than normal; later the trabeculation becomes coarse, and diffuse osteosclerosis occurs.

Naturally other features of this syndrome first catch the haematologist's attention. The patient is usually sent to his clinic because of increasing anaemia, and enlargement of the spleen is detected by the more mundane method of palpating the abdomen. If myelosclerosis is suspected, the patient's bones are *x*-rayed as part of the investigation. But the diagnosis is based on other findings. The blood count shows a leuco-erythroblastosis—that is, an increased white-cell count with early granulocytes and normoblasts present; platelets are usually normal in number or may be increased; megakaryocytes or fragments of these cells are also seen. Sternal puncture commonly provides little if any marrow, and what there is shows hypoplasia of all types of cell except the megakaryocytes. Spleen puncture carried out according to the technique of S. Moeschlin[4] provides a valuable clue. B. J. Leonard, M. C. G. Israëls, and J. F. Wilkinson[5] carried out spleen puncture on 13 patients and in every case found a typical "splenogram." In normal subjects most of the cells obtained by spleen puncture are lymphocytes, but in cases of myelosclerosis there are normoblasts and other earlier erythroblasts, myelocytes and metamyelocytes, and megakaryocytes; lymphocytes are reduced to 20–50% of normal. These gross changes are easily recognized and remind us that haemopoiesis is now going on in the spleen, mitotic figures being quite common. The splenogram of chronic myeloid leukaemia is different; most of the cells are granulocytes, including promyelocytes, with some myeloblasts; in polycythaemia vera the cells are nearly all polymorphs and lymphocytes. The diagnosis can be made certain by a bone biopsy, the iliac crest being a convenient site. The sections show the characteristic patchy replacement of the marrow with proliferating fibrous tissue and sometimes new bone. Illustrations of the various stages of this process have been published by B. J. Leonard and colleagues[5] and by D. R. Korst, D. V. Clatanoff, and R. F. Schilling.[6] But bone biopsy is rarely needed now; the other and more convenient methods of investigation mentioned above provide a diagnostic picture in almost every case.

[1] Dameshek, W., *Blood*, 1951, **6**, 372.
[2] Leigh, T. F., Corley, C. C., Jr., Huguley, C. M., Jr., and Rogers, J. V., Jr., *Amer. J. Roentgenol.*, 1959, **82**, 183.
[3] Mulcahy, F., *Proc. roy. Soc. Med.*, 1957, **50**, 100.
[4] Moeschlin, S., *Spleen Puncture*, 1951. London.
[5] Leonard, B. J., Israëls, M. C. G., and Wilkinson, J. F., *Quart. J. Med.*, 1957, **26**, 131.
[6] Korst, D. R., Clatanoff, D. V., and Schilling, R. F., *Arch. intern. Med.*, 1956, **97**, 169.
[7] Nelson, M. G., *Irish J. med. Sci.*, 1954, O.S., 488.
[8] Richmond, J., and Duncan, J. G., *Scot. med. J.*, 1956, **1**, 337.

The treatment of myelosclerosis is based on the recognition that the haemopoiesis in the spleen is responsible for an increasing proportion of the patient's supply of blood cells. Splenectomy is therefore not proper treatment, and destructive drugs like those used for the control of chronic myeloid leukaemia should also be avoided. The importance of accurate diagnosis is thus evident, since treatment suitable for chronic myeloid leukaemia will make the myelosclerosis patient worse. Sooner or later splenic haemopoiesis fails to maintain a satisfactory level of haemoglobin and then blood transfusion is needed. Leonard and colleagues suggest that it is sufficient to maintain the haemoglobin level at about 9 g. per 100 ml. (60%); this enables the patient to carry on well enough and avoids overloading the spleen with iron. The outlook for these patients is quite good, and with sensible management they can be kept in fair health for many years with the support of a monthly blood transfusion. In a few patients a haemolytic anaemia appears, and then splenectomy has to be considered. M. G. Nelson,[7] J. Richmond and J. G. Duncan,[8] and Leonard and colleagues[5] have described how the liver enlarges after splenectomy and eventually may fill the abdominal cavity; post-mortem examination shows that the liver sinusoids are enormously distended by erythropoietic foci. Splenectomy therefore rarely prolongs life and it is of doubtful value even in these haemolytic cases. The large spleen eventually causes serious mechanical embarrassment, and this, with the anaemia, makes the patient liable to succumb to pulmonary infections.

PLATELETS AND RADIATION DISEASE

Reports on the two serious radiation accidents which took place in 1958, one in Yugoslavia, and the other in the United States,[1 2] show that the treatment of casualties from such accidents has several special problems. These problems are also important in the treatment of atomic-bomb casualties and in the management of patients with cancer who, because of dissemination of their disease, have been subjected to radiotherapy over a wide area of the body.[3 4]

One such problem concerns damage to the blood-forming organs. These tissues are particularly sensitive to radiation; if a sufficient amount is irradiated the numbers of cells in the bone-marrow and lymphoid tissue may be drastically reduced and the tissues even rendered aplastic. This, in turn, leads to changes in the peripheral blood, with lymphopenia, granulopenia, thrombocytopenia, and anaemia developing in that order. Other tissues, notably the small intestine,[5] are depleted of cells by ionizing radiation, but, as profound changes in haemopoiesis take place with lower doses, it is the haematological damage which usually dominates the clinical picture.[1 2]

Animals given a sufficiently high dose of radiation will accept, as a graft, injected bone-marrow from another animal (and even from another species), and it has been shown that this graft will produce blood cells which function normally in the irradiated host.[6] A marrow graft appears, therefore, to be a logical answer to the problem, and five of the Yugoslav casualties were given such treatment. Grafts of this nature are accepted by the host only because his immune responses have been destroyed by the radiation. Animal experiments have shown, however, that as time passes immunity tends to return and an antigen-antibody reaction, known as "secondary disease" is likely to develop and may kill the recipient of the graft.[7] A marrow graft has been known to survive in man for several months,[8] but in spite of this the possibility of secondary disease must not be disregarded. A recent report by French workers[9] does, in fact, describe a syndrome very like secondary disease which developed in two children given marrow grafts after widespread irradiation for acute lymphoblastic leukaemia. In this instance the patients survived the secondary disease but the grafts ceased to function, and later the leukaemia relapsed. The possibility of secondary disease, therefore, makes bone-marrow grafting a hazardous procedure and it was not performed on any of the American casualties.[2]

The dangers of bone-marrow grafting call for a reassessment of the value of the transfusion of formed elements of the blood. The effects of the low white-

[1] Jammet, H., *et al.*, *Rev. franç. Ét. clin. biol.*, 1959, **4**, 210.
[2] Brucer, M., *The Acute Radiation Syndrome*, A medical report on the Y-12 accident, June 16, 1958. United States Atomic Energy Commission Report ORINS-25, Washington.
[3] Ferrebee, J. W., and Thomas, E. D., *Ann. intern. Med.*, 1958, **49**, 987.
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[5] Quastler, H., *Radiat. Res.*, 1956, **4**, 303.
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[9] Mathé, G., *et al.*, *Rev. franç Ét. clin. biol.*, 1959, **4**, 675.
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[13] Cronkite, E. P., Jacobs, G. J., Brecher, G., and Dillard, G., *Amer. J. Roentgenol.*, 1952, **67**, 796.
[14] Woods, M. C., Gamble, F. N., Furth, J., and Bigelow, R. R., *Blood*, 1953, **8**, 545.
[15] Bagdasarov, A. A., *et al.*, in *Progress in Nuclear Energy*, 1959, vol. 2, p. 180, London.
[16] Fliedner, T. M., Sorensen, D. K., Bond, V. P., Cronkite, E. P., Jackson, D. P., and Adamik, E., *Proc. Soc. exp. Biol. (N.Y.)*, 1958, **99**, 731.
[17] Tullis, J. L., Surgenor, D. M., and Baudanza, P., *Blood*, 1959, **14**, 456.
[18] —— *et al.*, *Science*, 1956, **124**, 792.
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[20] Haley, T. J., Riley, R. F., Williams, I., and Anden, M. R., *Amer. J. Physiol.*, 1952, **168**, 628.
[21] Andersen, A. C., *Radiat. Res.*, 1957, **6**, 361.
[22] —— Kohn, H. I., and Wooten, E., ibid., 1958, **9**, 86.

cell count can be treated by the transfusion of leucocyte concentrates, barrier nursing, and the judicious use of antibiotics. It might appear a comparatively simple matter to maintain the red-cell count artificially, but in many species, including man, haemorrhages are very important in the genesis of the anaemia. Changes in various haemostatic mechanisms have been reported, but the most important factor is the decrease in the numbers of platelets.[10] The thrombocytopenia follows a decrease in the numbers of megakaryocytes, and this, it has been concluded, is in its turn due to a block in the cellular division of the stem cell preceding the megakaryoblast.[11 12] Simple transfusions of whole blood have been of little value in experimental animals, though concentrates of platelets were found to correct defects in haemostasis.[13–15] Recent work on the subject[16] suggests, however, that though fresh platelets will control post-irradiation haemorrhage in rats the more convenient preparation of lyophilized platelet material is of no use for this purpose. Preparations derived by a new method,[17] which dispenses with lyophilization and preserves the platelets intact, may possibly be of use in the treatment of radiation disease. The method is complicated and entails a new principle of "closed-system centrifugation" during which the platelets are freed from plasma proteins.[18] They are eventually stored in gelatin and will keep for many months. Such preparations have been used in cases of marrow aplasia and thrombocytopenia caused by cancer chemotherapy, a condition somewhat similar to radiation aplasia.[17]

Platelet transfusions can act only as replacement therapy; they cannot stimulate an aplastic marrow to produce more platelets. Consequently repeated transfusions are necessary for the whole of the period when a dangerous thrombocytopenia is present. It is also possible that other factors besides thrombocytopenia are important in the haemorrhagic diathesis. A heparin-like anticoagulant, at one time thought to be important, may now be discounted,[2] but possible defects in the endothelial lining of the capillaries cannot be ruled out. Evidence for increased permeability of capillaries has been found in man 24 hours after as little as 100 r of local irradiation,[19] and various capillary changes have been reported in rats well before the time when thrombocytopenia would be expected.[20] Curious intravascular globules, which appear to contain a polysaccharide, have been found in some animal experiments,[21 22] and the degree of haemorrhage in individual animals was correlated with the size and amount of these globules. It was suggested that this material, acting as emboli and inducing endothelial damage, might, in the presence of a thrombocytopenia, cause haemorrhages. But it does not seem likely that such material is important in all species, for while it was plentiful in dogs and swine it was rarely seen in guinea-pigs, even though all three species are equally liable to post-irradiation haemorrhage.

A ROYAL EVENT

Despite the crowds outside Buckingham Palace, the television cameras, and the newscasters' words crackling round the world, the Royal Birth was just as much a family crisis and, when all was safely over, an occasion for family rejoicing as the birth of a child in any other household. True, the crisis was not quite of the nature of the emergency when last a reigning monarch gave birth to a baby. Then, so the *British Medical Journal* of April 15, 1857, informs us, Queen Victoria "was taken so suddenly with the pains of labour that a common hackney cab had to be despatched for Dr. Locock." Things were managed better in 1960, and for the Queen's medical attendants—Mr. J. H. Peel, Dr. V. F. Hall, Sir John Weir, and Lord Evans—there were no such undignified journeys as Dr. Locock had to suffer.

With the birth of the new Prince the Royal Family is strengthened not only in numbers but in all sorts of ways which may be intangible but which a strongly knit family can always make manifest. We can assure our Patron, the Queen, and our President, Prince Philip, Duke of Edinburgh, that this very happy Royal event will be a cause of great rejoicing among members of the British Medical Association.

GENETIC CLUES TO HISTORY

Soon after it had been shown that the blood groups are inherited as simple Mendelian characters, L. and H. Hirschfeld[1] observed in Salonika, where soldiers of the first world war and refugees from many parts of the world had been congregating, that different nations and different races showed different frequencies of the ABO genes. The B group is now known to be most frequent in India and in Central Asia, and the further people live from these parts the lower will be the frequency of the B gene. Thus in Europe the Basques have the lowest frequency of the B gene and the Russians the highest.[2 3] The MN system sh differences in gene frequencies in the Pacific area the ratio M to N is about 1 in the Chinese and well above 1 in the American Indians, and the Melanesians, Micronesians, aborigines.[3 4] Likewise Rhesus gene

variously distributed,[3 5-7] and the relatively high frequency of Rh-negative among the Brahmins in India, for instance, serves to emphasize their relationship with Europeans.[8]

The anthropological value of these characters depends much on whether they are stable from one generation to the next. Until recently the ABO blood groups were considered to be "neutral" characters—neutral, that is, in relation to the probability of their perpetuation from parent to child and, as such, anthropological markers *par excellence*. However, in 1953 I. Aird, H. H. Bentall, and J. A. Fraser Roberts[9] showed that the incidence of cancer of the stomach was greater in persons of blood-group A than in those of Group O. It is now known that the incidence of duodenal ulcer is about 40% higher in persons of blood-group O than in those belonging to groups A. B, and AB. Many other conditions have been investigated, and perhaps the most interesting association is that between pernicious anaemia and blood-group A.

In 1954 A. E. Mourant, director of the Medical Research Council's Blood Group Reference Laboratory, published his encyclopaedic survey of the distribution of the human blood groups.[3] He stressed that for practical purposes two classes of characters should be distinguished, those like the MN groups and, surprisingly, the Rhesus groups, which are fairly uniform over large areas and therefore seem to be stable systems suitable for tracing distant anthropological history, and those like the ABO groups, which show considerable differences even within otherwise uniform populations and can therefore possibly be used to trace relatively recent anthropological events. Even in Britain the ABO frequencies vary considerably. Their distribution reflects the Danish and Anglo-Saxon influence south and east, and the predominance of early British (or "Celtic") blood north and west. H. J. Fleure has remarked that the higher O incidence in the Glasgow area than in the rest of Scotland may be due to the many urbanized Highlanders there (from the West Highlands) and West Irish.[10] On the other hand a high A incidence in the region of Furness would reflect the many links with the Dano-Norse city of Dublin. Blood-group A is still very frequent in north-west Germany, Schleswig-Holstein, and Frisia, from where the Anglo-Saxons came. The frequencies of group A in Great Britain are expected to be higher where the Anglo-Saxons came with their wives as settlers rather than as military conquerors, because villages founded by them would be to a great extent endogamous. Very early cemeteries indicate the existence of such villages in the East Riding of Yorkshire, Norfolk, Cambridgeshire, north Northamptonshire, and Leicestershire, where the frequency of A is in fact high.[10] For the Solent and Hampshire, on the other hand, there are many indications of warlike invasion and struggle. Warrior bands would predominantly be male and take native girls; this might explain the stronger persistence of the O group in those parts of England.

Mourant's book, despite its completeness otherwise, did not tabulate the vast mass of data to be derived from the transfusion services. Now, under the auspices of the Nuffield Blood Group Centre, which is administered by the Royal Anthropological Institute, Mourant, Kopec, and Domaniewska-Sobczak have published exhaustive tables of all known ABO data and up-to-date maps of their distribution.[11] This monumental work surveys the outcome of just under 6 million blood-group estimations. It is a veritable treasure-house of information, of immense value for research.

Though a gene devoid of adaptive value may be an illusion, there is no need to assume that the ABO blood-groups have therefore lost their interest for the anthropologist.[12] While it is true that deductions covering very long periods will have to be made with caution, it is still possible to use the ABO groups in terms of human history over 2,000–3,000 years (rather than 20,000 years). The blood groups of old human remains have been determined since 1934, when W. G. and L. G. Boyd[13] first tested tissues from American and Egyptian mummies. Later, tests were carried out on ground bone.[14] A fascinating report of a Ciba Foundation Symposium[15] shows how the investigation of blood-group frequencies in certain areas of present-day Italy, combined with a knowledge of the distribution of blood groups in ancient times, may help to show where the Etruscans originally came from. In an Appendix K. Oakley and Madeleine Smith state the requirements of the British Museum (Natural History) for determining the blood groups in human bones from current and future excavations at Etruscan and Roman sites.

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[2] Boyd, W. C., *Tabul. biol.* ('s-Grav.), 1939, **17**, 113.
[3] Mourant, A. E., *The Distribution of the Human Blood Groups*, 1954, Oxford.
[4] Birdsell, J. B., and Boyd, W. C., *Amer. J. phys. Anthrop.*, 1940, **27**, 69.
[5] Wiener, A. S., Sonn, E. B., and Belkin, R. B., *Proc. Soc. exp. Biol.*, 1943, **54**, 238.
[6] Etcheverry, M. A., *Dia méd.*, 1945, **17**, 1237.
[7] Mourant, A. E., *Nature (Lond.)*, 1947, **160**, 505.
[8] Sanghvi, L. D., and Khanolkar, V. R., *Ann. Eugen. (Lond.)*, 1950–51, **15**, 52.
[9] Aird, I., Bentall, H. H., and Roberts, J. A. F., *Brit. med. J.*, 1953, **1**, 799.
[10] Fleure, H. J., in Kopec, A., *Advanc. Sci.*, 1956, **51**, 200.
[11] Mourant, A. E., Kopec, A. C., and Domaniewska-Sobczak, K., *The ABO Blood Groups*, 1958, Oxford. (Blackwell Scientific Publications, 42s.).
[12] Roberts, J. A. F., *J. roy. anthrop. Inst.*, 1958, **88**, 115.
[13] Boyd, W. G., and Boyd, L. G., *Proc. Soc. exp. Biol.*, 1934, **31**, 671.
[14] Candela, P. B., *Amer. J. phys. Anthrop.*, 1936, **21**, 429.
[15] *Ciba Foundation Symposium on Medical Biology and Etruscan Origins*, ed. G. E. W. Wolstenholme, and C. M. O'Connor, 1958, London (J. & A. Churchill, 45s.).

TRIAL OF LIVE POLIOMYELITIS VACCINE

The evidence is mounting that oral poliomyelitis vaccine may give a stronger and more lasting immunity than vaccines of the Salk type. Some months ago we published the results of the important Singapore trial[1] of Sabin's Type II vaccines, and a few weeks ago we reviewed[2] recent reports from other parts of the world. Now, as the Minister of Health announced in Parliament last week, the Medical Research Council is to

[1] Hale, J. H., Doraisingham, M., Kanagaratnam, K., Lee, L. H., Leong, K. W., and Monteiro, E. S., *Brit. med. J.*, 1959, **1**, 1541.
[2] Ibid., 1959, **2**, 624.

carry out small-scale trials of the Sabin vaccine in selected areas of Britain.

In the absence of epidemics of poliomyelitis, the only way of assessing the degree of protection given by a vaccine is to estimate the neutralizing antibodies in the serum and to find out whether or not the attenuated viruses of which the vaccines are made establish themselves in the intestine. Even the proposed small trials will therefore necessitate much laboratory work, and probably not more than 300 or 400 children will take part in this investigation. With the advice of the family doctors concerned medical officers of health of the areas where the trials are to take place will select the children, in groups of 20 or so, from among those whose parents agree to their receiving the vaccine. The children will be 6–9 months of age and, of course, they will not have already received any injections of Salk vaccine. Some parents may not feel inclined to agree to their children entering this trial, and others will probably wish to obtain the views of their family doctor before agreeing. Since the trial is designed to find out the best system of dosage of oral vaccines against poliomyelitis no guarantee can be given that the dose of vaccine taken by any particular child will produce a lasting immunity, but it will be helpful for parents to know that the Sabin vaccine which is to be used has already been widely tested and found to be safe and convenient. Further essential information about the vaccine can be obtained only by carefully conducted trials such as that now to be undertaken by the Medical Research Council.

ALCOHOLIC CARDIOMYOPATHY

Excessive consumption of alcohol may result in myocardial disease.[1–3] The clinical manifestations may vary from the type of cardiac failure with higher than normal output found in beriberi heart disease, which responds to thiamine, to the low-output type of cardiac failure associated with hypertrophy and fibrosis of the myocardium and not or scarcely responding to thiamine.[4–6] It is the latter type that is more commonly seen in the Western Hemisphere and may easily be overlooked, because clinically it resembles other forms of cardiomyopathy or coronary arterial disease.

W. Brigden[5] in 1957 described 13 cases of heart disease in patients who were heavy drinkers and had no other apparent cause for the myocardial failure. The patients' ages ranged from 41 to 69; all but one were men; seven drank nothing but beer, with an average consumption of 10 pints (5.7 l.) a day for 10 to 40 years. The six other patients drank one or more bottles of spirits a day for 10 to 20 years. Symptoms and signs appeared earlier and were more severe in those who drank spirits. Nutrition was uniformly good and it was often difficult to elicit the true history of alcoholic habits. All presented with dyspnoea on exertion, and in several this was accompanied by palpitation. None had chest pain or syncope. Cardiac failure soon appeared after the onset of symptoms, with generalized enlargement of the heart. Tachycardia was usual and irregularity from extrasystoles or atrial fibrillation common. The pulse tended to be small, without evidence of hypertension. Triple rhythm associated with myocardial failure was common. The electrocardiogram confirmed the arrhythmia due to atrial fibrillation in five cases. In sinus rhythm the P waves tended to show slight right atrial preponderance. The QRS–T complexes showed various degrees of myocardial damage. The T wave was often small and inverted in the left chest leads, and left bundle-branch block developed in four cases. Radiography showed from slight to gross cardiomegaly. The myocardium at necropsy showed the presence of small patches of fibrosis in the left ventricle with, in one case, a recent small area of necrosis in the base of the papillary muscle, with overlying mural thrombus. There was no evidence of coronary arterial disease.

More recently W. Evans[7] has described 20 patients who had been assembled because of bizarre symptoms and signs and an abnormal electrocardiogram, and before a history of alcoholism had been obtained. The clinical features were similar to those described by Brigden, except that chest pain occurred in six, though it was not typical of that associated with coronary arterial disease in its site, character, or response to either exercise or rest. In 17 of the 20 patients the electrocardiogram showed changes confined to the T wave. Evans divides these into three groups—the "dimple" T wave, the "cloven" T wave, and the "spinous" T wave—and considers they are characteristic of alcoholic cardiomyopathy. Other abnormalities of the electrocardiogram included auricular fibrillation, extrasystoles, paroxysmal tachycardia, transient bundle-branch block, and depression of the S–T segment. Abstinence from alcohol in some cases was associated with a change of the electrocardiogram towards a normal pattern.

In Brigden's series, the results of treating patients in established heart failure with digitalis and diuretics was moderately good at first, and there was little, if any, difference in the response of patients who received large doses of thiamine and those who had none. Repeated attacks of myocardial failure showed a progressively diminishing response to therapy. The duration of symptoms was from two and a half to five years, and five out of the 13 patients died.

The myocardium, like the liver, appears to be vulnerable to a high intake of alcohol over a long period of time, and this beverage should be considered as a possible aetiological factor in a patient who presents with cardiomegaly and heart failure or an electrocardiogram with abnormal T waves and in whom there is no obvious cause for these abnormalities. In early cases total abstinence may possibly halt or reverse the disease.

[1] Mackenzie, J., *Diseases of the Heart*, 1908, London.
[2] Sansom, A. E., *Diseases of the Heart and Thoracic Aorta*, 1892, London.
[3] Steell, G., *Textbook on Diseases of the Heart*, 1906, Manchester.
[4] Benchimol, A. B., and Schlesinger, P., *Amer. Heart J.*, 1953, **46**, 245.
[5] Brigden, W., *Lancet*, 1957, **2**, 1179 and 1243.
[6] Weiss, S., and Wilkins, R. W., *Ann. intern. Med.*, 1937, **11**, 104.
[7] Evans, W., *Brit. Heart J.*, 1959, **21**, 445.

PARALYSIS IN MOROCCO

Reliable information is now available about the recent distressing outbreak of poisoning in Morocco, which afflicted about 10,000 of its inhabitants late last summer. According to an account of the epidemic by H. V. Smith and J. M. K. Spalding[1] the toxic agent was *ortho*-cresyl phosphate, a substance which is used in aeroplane engine oils to prevent the deleterious effects of great heat, such as the formation of deposits on valve stems and sparking-plugs. Apparently unwanted stocks of oil containing the *o*-cresyl phosphate found their way, through the agency of mistaken or unscrupulous merchants, into oil which was sold as cooking fat. The consumers of such fat soon developed paralysis in the legs, and later the hands were often affected. The condition was not fatal, and the symptoms were sometimes mild. Recovery was slow, and it is feared that in some cases the injuries may be permanent.

Besides its inclusion in lubricants *o*-cresyl phosphate is used for various other purposes, including the manufacture of plastics. Outbreaks of poisoning have been frequent and well authenticated, early ones occurring in many parts of the U.S.A. in 1930. On that occasion the paralysis appeared in thousands of consumers of certain brands of Jamaica ginger extract, which were adulterated with tri-cresyl phosphate.[2] The ginger extract was used as a source of alcohol, either neat or diluted with soft drinks, or as a cure for dyspepsia. From the evil effect of one well-known beverage called "Ginger Jake" the name "Jake" paralysis was applied. It is remarkable that after a lapse of 30 years "Jake" should have turned up in such a different disguise to claim a fresh batch of victims. Three cases of accidental poisoning in industry were reported in Great Britain in 1944.[3]

Research into the mode of action of *o*-cresyl phosphate has indicated that it causes injury to the myelin sheath, but the specificity of this lesion is doubted.[4] Some animals, such as the calf and mature hen, are vulnerable, but others, such as the rabbit and young chicken, are very resistant. The commercial substance, generally described as tri-*ortho*-cresyl phosphate, is never pure, and the impurities may be even more toxic than the pure substance. It has been suggested that the toxicity is due to interference with the action of the enzyme pseudocholinesterase. Tests on a wide range of substances, however, have shown that neurotoxicity and enzyme inhibition do not always run parallel.[5] Another theory is that tri-*o*-cresyl phosphate may antagonize the action of vitamin E. Thus the paralysis seen after dosing lambs with the poison is superficially similar to "stiff-lamb disease," a manifestation of vitamin-E deficiency seen in the field.[6] Dosing lambs with vitamin E, however, will not cure them, or even completely protect them, from the injurious effects of tri-*o*-cresyl phosphate. Though the exact mechanism of the injury to the nerves remains uncertain, it is clear that many derivatives of cresol are poisonous, and that they may obtain access to the body, either orally or through the skin, in very different vehicles. People who use them commercially have a great responsibility that their products do not endanger the public.

[1] Smith, H. V., and Spalding, J. M. K., *Lancet*, 1959, **2**, 1019.
[2] Burley, B. T., *J. Amer. med. Ass.*, 1932, **98**, 298.
[3] Hunter, D., Perry, K. M. A., and Evans, R. B., *Brit. J. industr. Med.*, 1944, **1**, 227.
[4] Cavanagh, J. B., *Lancet*, 1959, **2**, 1188.
[5] Susser, M., and Stein, Z., ibid., 1959, **2**, 1089.
[6] Draper, H. H., James, M. F., and Johnson, B. C., *J. Nutrit.*, 1952, **47**, 583.

PEANUTS AND HAEMOPHILIA

Severely affected haemophilic patients often note that episodes of spontaneous bleeding come in cycles. A severe haemarthrosis may be accompanied, or rapidly followed, by spontaneous bruising or haematuria. Several joints may be affected at any one time. In intervening periods the patient may be very well and even withstand minor trauma which would cause bleeding at a less favourable time. In the laboratory no known haemostatic test is altered in the good or bad phases.

Thus a claim for clinical effectiveness of any substance in haemophilic patients is difficult to substantiate. The patient may take the material in a "good" phase or at the end of a "bad" phase and claim much relief, while if he had taken the material at another time he might have formed a less optimistic view. Moreover, patients with chronic incapacitating diseases tend to feel relief from new treatment, but the relief is not always so apparent to the objective eye of their medical advisers.

These difficulties should not prevent the careful investigation of a substance thought to be effective in the treatment of haemophilia. Such a claim has been made by H. B. Boudreaux and V. L. Frampton[1] for the use of peanut derivatives taken by mouth. One of the authors is himself a haemophiliac, and he has found that the ingestion of peanuts or peanut flour has aborted attacks of haemarthrosis and when taken continuously has prevented their occurrence. The material has been tried on three other volunteers, with similar results. Eating peanuts does not affect laboratory results on the patient's blood, and the effective substance is not in the fatty part of the peanut but in the residual meal obtained after extraction with hexane.

Ingestion of the material does not correct the haemophilic clotting defect, but if it reduces the incidence of spontaneous bleeding it would do much to alleviate the lives of severely affected patients. It is to be expected that many haemophilic patients will try this simple treatment, and they would be well advised to do so with the co-operation of their medical advisers and of the Haemophilia Society. In this way an objective record of episodes of bleeding can be kept, accurate descriptions of the type and amount of peanut product used can be available, and the records of all the patients' experiences can be pooled and assessed.

An article on the Royal Commission's Report appears in this week's *Supplement*.

[1] Boudreaux, H. B., and Frampton, V. L., *Nature (Lond.)*, 1960, **185**, 469.

Clinicopathological Conference

A CASE OF JUVENILE CIRRHOSIS

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a girl with juvenile cirrhosis due to Kinnier Wilson's disease (Case No. 80,877; P.M. No. 8,738). She was treated by porta-caval anastomosis.

Clinical History

Professor SHEILA SHERLOCK: We are considering to-day the case of a young woman suffering from a rare disease, but one which has aroused great interest in workers of many disciplines. She was a shop assistant aged 17 when I first saw her in 1956. She had left school in 1953—"inefficient in everything"—and had only attained Standard II. In 1954 she found herself unable to perform fine movements, her handwriting had deteriorated, and she noticed her hands clenched involuntarily. In 1955 the development of tremor and occasional unsteadiness in walking led to her consulting Dr. S. Nevin, at the Maida Vale Hospital for Nervous Diseases. She was found to have dysarthria, tremor, and to show choreiform movements. Examination of the eyes showed a brownish ring round the cornea (Kayser–Fleischer ring). She also showed splenomegaly. A diagnosis of Kinnier Wilson's disease (hepato-lenticular degeneration) was made.

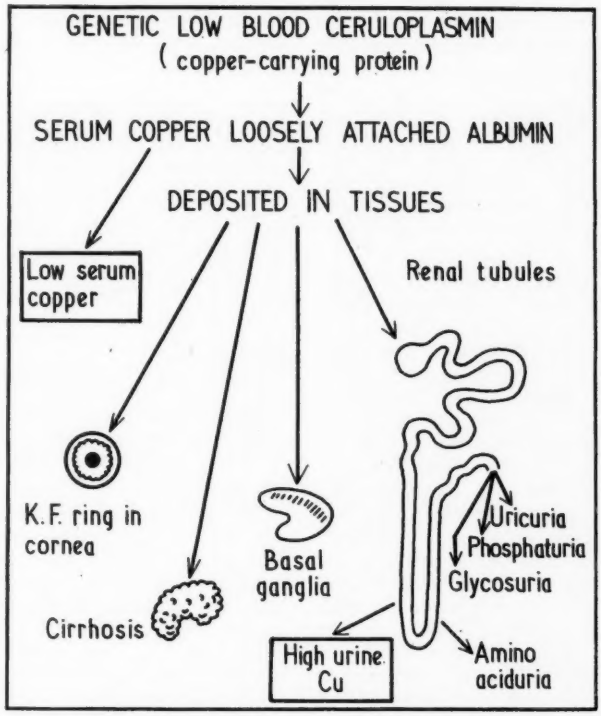

FIG. 1.—A possible explanation of the clinicopathological features of Kinnier Wilson's disease (hepato-lenticular degeneration).

EVIDENCE OF METABOLIC UPSET

This condition is believed to be due to an inborn deficiency in serum ceruloplasmin (Fig. 1). This protein is used for the transport of copper, and, in its absence, copper is transported loosely attached to albumin. The serum copper level is low. The copper is easily split from its attachment to albumin and is deposited in the tissues. In the cornea it produces the Kayser–Fleischer ring; deposits in the basal ganglia result in tremor, ataxia, and so on; and copper in the kidneys seems to be responsible for various renal tubular defects. Professor J. N. Cumings kindly carried out certain investigations of copper metabolism and showed that the serum copper oxidase (ceruloplasmin) activity was absent. The serum copper was reduced from the normal of 90–160 μg./100 ml. to 47 μg./100 ml. The 24-hour copper excretion was raised from the normal of 10–70 μg. to 375–533 μg. Wilson's disease is the only condition in which a low serum copper level is associated with increased urinary copper.

On a later occasion renal tubular function was assessed. There was glycosuria when the blood glucose level was less than 100 mg./100 ml. The blood uric acid was reduced to 1.1–0.3 mg./100 ml. The serum calcium level was normal, but the serum phosphate was reduced to 2 mg./100 ml. Radiographs of bone were normal. There was a fairly generalized aminoaciduria. These findings suggested a tubular disturbance. The patient did, however, acidify urine normally, for when given 50 mEq ammonium chloride the *p*H of the urine fell to 5.

Wilson's disease is believed to be inherited as an autosomal recessive. Sufferers are often the result of cousin marriages. There was no known consanguinity in our patient's family. Her parents and two brothers were normal. The serum copper oxidase level was estimated in them. In one brother only was a slightly reduced value found.

The diagnosis of Wilson's disease seemed certain and treatment was started with B.A.L. (dimercaprol). This results in an increased excretion of copper in the urine and levels of 1,052 μg. in the 24 hours were found after this treatment. There was definite clinical improvement, the involuntary movements almost disappeared, and she could walk better.

PORTA-CAVAL ANASTOMOSIS

In April, 1956, she was readmitted to the Maida Vale Hospital for further dimercaprol treatment, when she had a sudden brisk haematemesis and she was transferred to Hammersmith Hospital. Further haemorrhage necessitated the passage of the Sengstaken oesophageal compression tube.* Whenever the tube was

*See *Brit. med. J.*, 1960, **1**, 227.

withdrawn the bleeding recommenced, and 22 pints (12.5 litres) of blood were transfused before the bleeding ceased. The haemorrhage was believed to be coming from oesophageal varices secondary to the cirrhosis of the liver which is an almost constant accompaniment of Wilson's disease.

The question of porta-caval anastomosis for the relief of the portal hypertension now arose. Clinically she seemed a good subject for the operation. She had no ascites, no jaundice (serum bilirubin 0.8 mg.), and the serum albumin level was 4.4 g. per 100 ml. A splenic venogram showed a normal portal vein suitable for anastomosis with the vena cava, but there were many collateral channels running up to the oesophagus (Fig. 2). The intrasplenic pressure, taken as a measure of the portal pressure, was raised to 35 mm. Hg (normal 6–12). There is a strong possibility that neuropsychiatric complications will develop in cirrhotic patients having a porta-caval anastomosis, presumably due to the by-pass of nitrogenous substances absorbed from the intestine, round the liver, to the brain. A high-protein diet was therefore given for ten days. There were no clinical changes and the electroencephalogram did not show the slow waves associated with impending hepatic coma. In June, 1956, a porta-caval anastomosis was performed end-to-side. The operation was successful in that the spleen decreased in size, the intrasplenic pressure fell to a normal value (7 mm. Hg), and a further splenic venogram showed a patent shunt (Fig. 3). After operation, however, her neurological condition worsened and it was uncertain whether this was a consequence of the Wilson's disease or of the porta-caval anastomosis.

In February, 1957, she was readmitted because her neuro-psychiatric condition had deteriorated, particularly her speech. She was again tested with a high-protein diet, which did not produce an exacerbation. Neomycin improves the neuro-psychiatric condition of patients after porta-caval anastomosis. This therapy had no effect on our patient and it was concluded that the changes were due to the Wilson's disease. At this time, penicillamine—discovered by Dr. John Walshe as a good chelating agent in Wilson's disease—became available. This has the advantage over dimercaprol of oral administration. It was continued until her final admission to hospital in February, 1959. She was also given oral potassium sulphide, which combines with copper in the intestine, forming insoluble copper sulphide which is not absorbed.

In September, 1958, she had a urinary infection and with it hyperpyrexia, a haemorrhagic eruption, and generalized oedema. This was thought to be a reaction to penicillamine and subsided on antihistaminic treatment.

TERMINAL ILLNESS

In November, 1958, she complained of generalized aches and pains with increasing swelling of the eyes and jaundice. She was drowsy and itching. On January 1, 1959, she was transferred from the Maida Vale Hospital to Hammersmith Hospital. Examination showed fetor hepaticus. This finding is not unusual in patients after porta-caval anastomosis. The speech was slurred, the eyes swollen, but there was no tremor. The blood ammonium level was 1.3 μg./ml., which is only slightly raised over the upper limit of normal (1 μg./ml.). The electroencephalogram did not show the slow waves of hepatic coma. The serum bilirubin was greatly increased to 12.3 mg., the serum albumin reduced to 2.6 g., and the serum globulin raised to 3.2 g. Electrophoretic analysis of the serum proteins showed an increase in the gamma component. A barium meal showed no oesophageal varices. The pruritus improved with antihistaminics and was thought to be due to penicillin sensitivity. The high serum bilirubin level with low serum albumin and raised gamma globulins suggested an active type of cirrhosis. This type of patient often improves with corticosteroid therapy, and the patient was therefore given dexamethasone. This therapy was followed by severe abdominal pain suggesting the lighting up of a peptic ulcer. She was given "aludrox" (an aluminium hydroxide gel). On February 8 she was very restless and delirious, and on February 9 right-sided, followed by generalized, fits lasted 36 hours. She was given 3 gr. (0.2 g.) of sodium phenobarbitone intramuscularly. This was followed by a deep coma from which she did not recover. She was treated with neomycin and intravenous glucose therapy, and attention was paid to the development of potassium and magnesium deficiency. She continued in coma until March 8, when fresh blood was aspirated from the stomach and she died. The coma had never been typical of that seen with liver failure.

Clinical Diagnosis

(1) Hepato-lenticular degeneration.
(2) Functioning porta-caval anastomosis.
(3) Jaundice, ? hepatic failure.
(4) Coma, ? cause.
(5) Terminal erosive gastritis.

Post-mortem Findings

Dr. A. G. E. PEARSE: The post-mortem examination was performed 27 hours after death by Dr. S. Wilson. The body was that of a woman, height 5 ft. 10 in. (1.75 m.); weight 7 st. 8 lb. (48 kg.). The general findings were deep jaundice; oedema of, and around, the eyes; cirrhosis of the liver; a surgical porta-caval anastomosis: areas of softening in the region of the basal nuclei; and gastric erosions.

The *liver* was underweight (1,010 g.) and showed gross cirrhosis of the post-necrotic type. In colour it was dark green and it was composed of nodules of liver tissue varying from 5–10 mm. in diameter, separated from one another by thick fibrous septa. Histologically (Fig. 4), small nodules of regeneration were present and these were in some cases broken up almost into individual cells by the proliferating fibrous tissue. Perl's reaction showed a very large amount of iron-containing pigment, accompanied by a lesser amount of bilirubin, some of which had been deposited in the form of small bile thrombi. The *gall-bladder* was filled with small pigment stones. An anastomosis of the portal vein into the inferior vena cava had been made. This was intact and the anastomotic opening measured 1 cm. in diameter. No collateral veins were demonstrated.

The *brain* was of normal weight (1,184 g.) and showed softening in the region of the right basal ganglia. The left half of the brain was sent away, uncut, for chemical investigations. Histologically, there were no abnormalities in the neurones of the cerebral cortex, the cerebellum, or the basal ganglia, but there was some gliosis in the thalamus. The *pituitary gland* was macroscopically normal, but microscopically there was diffuse hyperplasia of the mucoid (basophil) cells. A

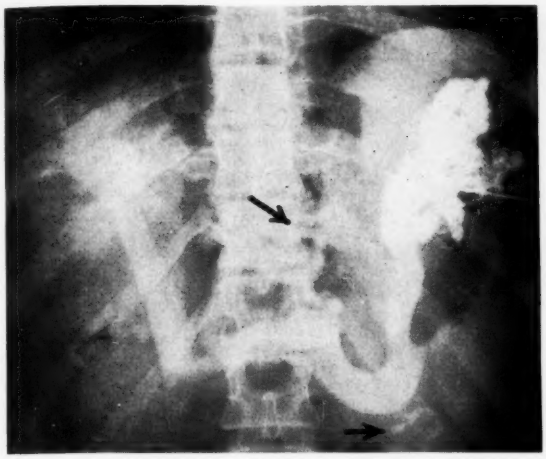

FIG. 2.—Splenic venogram obtained by injecting radio-opaque material percutaneously into the spleen. The pool of dye in the splenic pulp is seen and the splenic and portal veins are outlined. A large portal collateral circulation is seen running upwards from the splenic vein towards the oesophagus and inferiorly along the splenic capsule. The intrahepatic vascular pattern is abnormal.

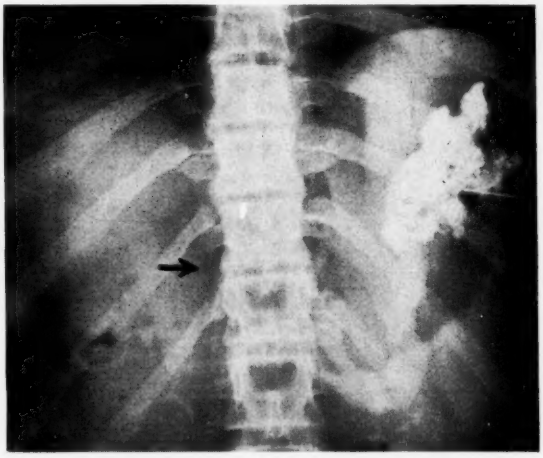

FIG. 3.—Splenic venogram obtained after porta-caval anastomosis. The pool of dye in the spleen is again seen. The splenic vein is outlined and the portal vein faintly so. The porta-caval anastomosis is patent, the inferior vena cava being noted as a vertical shadow to the right of the vertebral column. The collateral circulation is no longer visible. The intrahepatic veins are not shown.

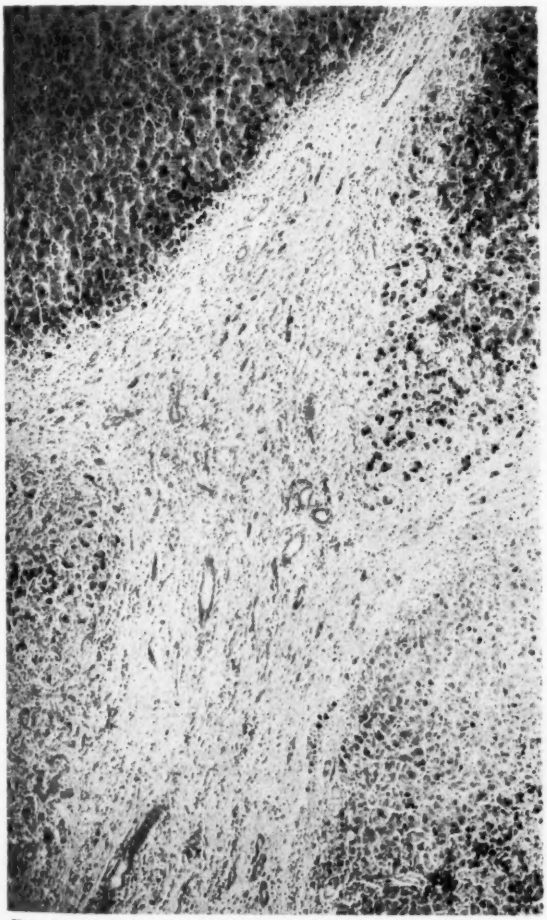

FIG. 4.—Liver showing cirrhosis and patchy distribution of iron-containing pigment in liver cells. (×57.)

FIG. 5.—Pituitary showing a group of mucoid (basophil) cells, all of which are fully granulated. In the centre of the field is a binucleate mucoid cell suggesting increased activity of the cells of this series. (×868.)

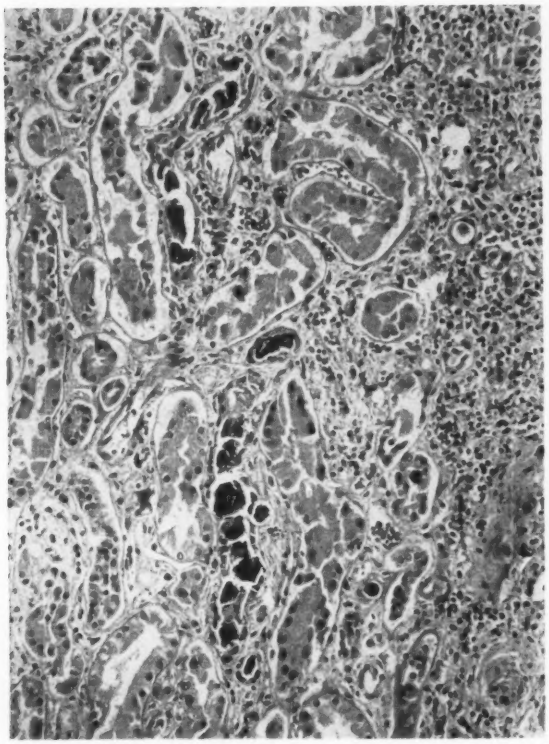

FIG. 6.—Kidney showing bile-stained protein casts in distal convoluted tubules. (×100.)

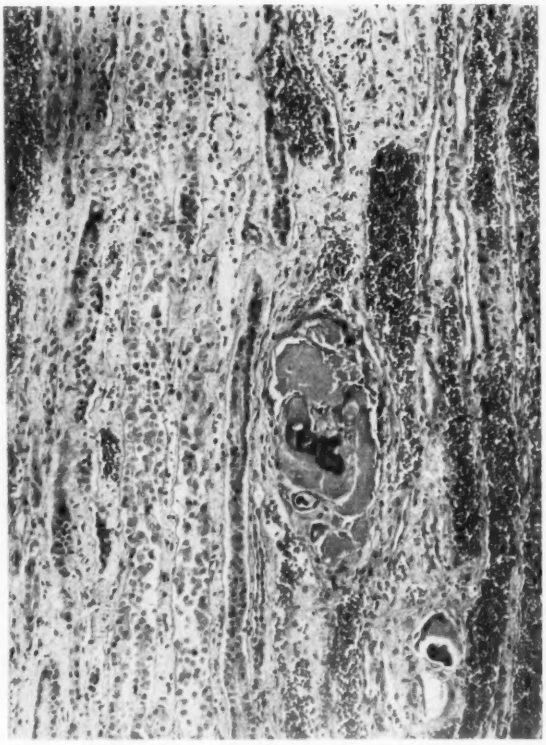

FIG. 7.—Kidney showing amorphous and crystalline deposits of calcium phosphate lying in the interstitial tissues of the medulla. (×120.)

FIG. 8.—A liver biopsy from an untreated case of Wilson's disease. The cells contain greenish-black deposits of copper stained by the rubeanic-acid procedure. (×603.)

FIG. 9.—Left knee-joint, showing typical osteochondritis dissecans.

binucleate mucoid cell, signifying response to some abnormal stimulus, is shown in Fig. 5.

The *kidneys* (each weighed 150 g.) were deeply bile-stained and showed patchy pyelonephritis with one small abscess visible at the lower pole of the left kidney. The pelvis and ureter on each side appeared normal. Histologically (Fig. 6), bile casts were present in the collecting tubules and an interstitial infiltrate of lymphocytes and macrophages was present. One section showed a small acute abscess. There were also areas of nephrocalcinosis (Fig. 7).

The *oesophagus* appeared normal, there being no evidence of varices. The *stomach* showed two acute ulcers, one on the posterior surface which involved the mucosa only, and one on the anterior surface which had perforated the whole thickness of the muscle wall. A small amount of blood clot was present in the stomach and in the peritoneal cavity.

The *left knee-joint* was removed and examined at St. George's Hospital, where osteochondritis dissecans was found to be present. Other pathological findings were: (1) Bilateral pulmonary oedema (right lung 472 g., left lung 501 g.); (2) altered blood filling the entire large intestine; and (3) an enlarged spleen (490 g.). The *heart* (389 g.), *pancreas, bladder, suprarenals* (5 g. each), and *thyroid* (19 g.) appeared normal.

Presence of Copper in the Tissues: Histochemical tests for copper were done on renal and liver biopsies in June, 1956, but these were entirely negative. Similar tests were carried out on the brain, liver, and kidney at necropsy, and these were also entirely negative. Assay for copper by Professor J. N. Cumings at the Institute of Neurology showed the highest level of copper present in any tissue examined to be 16.59 mg./100 g. dry weight in the grey matter of the cerebellum. Average figures recorded for the brain were a little higher than normal, but for the liver and kidney the figures were within the normal range.

Pathologists' Summing-up

Comparison between the earlier liver biopsy (June, 1956) and that just before death, and with sections obtained post-mortem, showed that there was a progressive fibrosis of the liver in spite of the presumed successful removal of copper. There were only moderate attempts at regeneration. Between 1956 and 1959 the amount of iron present increased enormously, and at least some of this must be attributed to the large number of blood transfusions she received.

Discussion

Professor SHEILA SHERLOCK: I am glad that necropsy showed that most of the copper had been removed from the body. We were never quite certain that our therapy had been adequate. An analogy may be drawn with the removal of iron from the tissues in haemochromatosis by repeated venesections. In both conditions the heavy metal in the tissues, whether iron or copper, seems to be easily mobilized.

You might be interested in knowing some of the historical landmarks in this rare and interesting disease. Kinnier Wilson described it in 1912 as "progressive lenticular degeneration, a familial nervous disease associated with cirrhosis of the liver." In 1902 Kayser described the corneal ring and in 1903 Fleischer associated it with nervous disease. The first implication that copper was involved was in 1913 by Siemerling and Orloff. Dr. A. J. Glazebrook in Edinburgh in 1945 found increased amounts of copper in the liver of a patient with Wilson's disease, and this was the stimulus for all the further developments. Professor McMichael will remember Dr. B. M. Mandelbrote, who was once his houseman, and who in 1948 observed an increase in urinary copper. Also in 1948 Laurell and Holmberg in Sweden identified the copper-carrying serum protein, ceruloplasmin. Professor J. N. Cumings, again in 1948, showed the high level of copper in the liver. Denny-Brown and Uzman in Boston in 1945 showed aminoaciduria and demonstrated the improvement with dimercaprol treatment. Dr. Malcolm Milne studied the relationship of aminoaciduria to copper excretion, and then Dr. A. G. Bearn, who also worked here, was the first to show the increased absorption of copper from the gut and was also the first to show that there were diminished amounts of ceruloplasmin in the blood in this condition. And then, finally, the last major development has been by Dr. John Walshe, of University College Hospital and Cambridge, introducing penicillamine as an oral means of treatment.

JUVENILE CIRRHOSIS

Now you may all think this is a terribly rare disease, but it has implications for everyone. It involves me particularly in its association with juvenile cirrhosis. I would urge all of you, whenever you see any patient with juvenile cirrhosis, to bear Wilson's disease in mind, as the cirrhosis may not be accompanied by neurological changes. It is your duty in all cases of juvenile cirrhosis to look very carefully for a Kayser–Fleischer ring, to take a good family history, particularly of consanguinity, and measure perhaps the plasma uric acid and also, if possible, the serum ceruloplasmin (copper oxidase). Finally, if a liver biopsy is done on a patient with juvenile cirrhosis, a small portion should be freshly fixed in alcoholic rubeanic acid so that staining for copper (Fig. 8) may be done. You cannot go back again later and try to stain the sections for copper. We've been caught here only this year with such a case: a young girl I saw last year with a cirrhosis which seemed to bear no relation to Wilson's disease was, a year later, developing the classical neurological changes of Wilson's disease. We quite missed the diagnosis a year ago.

Dr. I. DONIACH: Could I ask whether the corneal rings altered as a result of the treatment with penicillamine here?

Professor SHERLOCK: Well, they are supposed to go with the penicillamine. In this patient they persisted right to the end, but were less obvious.

Professor E. J. KING: In that second case you mentioned, was the copper oxidase estimated?

Professor SHERLOCK: I hoped you wouldn't ask that. It was done and it was normal. Of course this is where you get into difficulties with this disease. A group do have a normal copper oxidase, and certainly this patient clinically has Wilson's disease. The ceruloplasmin in this particular girl has been fractionated by Dr. Broman in Uppsala and found to be normal. It just shows that my little scheme of Wilson's disease (Fig. 1) isn't the whole story.

Professor J. McMICHAEL: Dr. Milne, I think you have credit for a contribution to this subject?

Dr. M. D. MILNE: I think it was rather a kindness on Professor Sherlock's part. There was just one little point on which I disagreed with her: she said that this was the only disease where there is a low serum copper with a

high urinary copper. That should be qualified—in the absence of proteinuria—because it does occur constantly in the nephrotic syndrome, where ceruloplasmin leaks across the glomeruli and you do get there a low serum copper with a high urinary copper, but that of course is easily distinguished by the proteinuria.

NEUROLOGICAL DAMAGE

One thing I am always puzzled about in Wilson's disease—and this is very neurological—is the question of intelligence. All the cases of Wilson's disease I've seen have been rather unintelligent. Now this is very much against the original description of Kinnier Wilson. He always made the point that these patients usually did not show intellectual deterioration, and often an injustice was done to them. In fact he has a classical picture in his book showing a very vacant-looking girl, with the subscript, "Note the intelligent look in her eyes." I was never able to see this intelligent look; I thought that probably it was because I had never been trained as a neurologist. I would like to ask Dr. Pallis what is the present consensus of opinion of the intellectual faculties in Wilson's disease, because I have never seen these patients show any marks of genius.

Dr. C. PALLIS: Many patients with this disease are, I think, mildly demented, especially in the later stages of the illness. Others show transient psychotic states. In many intellectual loss may be a lot less marked than their fatuous facial appearance would lead one to believe. But what is more interesting is the tremor in this condition. Professor Sherlock prefaced her remarks by saying that, when she first addressed these clinicopathological conferences, she used to shake like a leaf. I was hoping that she was going to say, "like a case of hepato-lenticular degeneration," and that she would proceed to demonstrate the tremor. The tremor may be of a rather peculiar kind. Some cases show a regular, rhythmical tremor, present at rest and aggravated by excitement. Others show little tremor at rest, but a marked action tremor. The majority probably show both types of involuntary movement: they have a mild Parkinsonian-like tremor at rest which becomes accentuated when they hold their hands outstretched or bring the finger to the tip of the nose. These clinical features are not unexpected. The lesions may be more disseminated than was originally thought. The dentate nuclei of the cerebellum are occasionally involved, as well as the caudate nucleus and putamen.

Professor MCMICHAEL: I must say I am learning a lot from this particular conference. I had the idea that the copper was the damaging agent and that the trouble depended on failure to bind copper to ceruloplasmin. Now all the copper was apparently successfully removed, as judged from the biopsy material, in 1956, and the disease was not arrested. Are we overlooking something, or am I completely wrong?

Professor SHERLOCK: I am not sure you are right that *all* the copper was removed by 1956, because all we have is the one kidney biopsy to show that the copper was removed; the liver was not in fact stained for copper at that stage, and often the kidney doesn't show very much. As regards progression, adequate treatment may not stop the progression of the cirrhosis. Experienced observers are now finding that patients, apparently successfully treated with dimercaprol, are turning up in liver failure. At a certain stage the cirrhotic process is irreversible.

Professor KING: Is there any counterpart to this in which you can demonstrate excess exposure to copper or accumulation in the tissues—in industry, for instance, or experimentally in animals?

Professor MCMICHAEL: I think there was something experimentally in the early 1930's from Aschoff's laboratory, where a copper salt was used to produce both cirrhosis and lenticular degeneration. The idea wasn't followed up in man; I think there was some species specificity, but I should need to refresh my memory on that one.

Dr. PEARSE: It has been repeated by Howell* in Birmingham on rats, feeding them with maize and copper. The conclusions I don't know, except that you can demonstrate copper afterwards in the liver, which didn't look very abnormal to me, judging from the pictures. What the liver function was, I don't know.

ROLE OF CERULOPLASMIN

Professor KING: Has anyone ever hazarded the guess that the symptoms might be due to a lack of ceruloplasmin?

Professor SHERLOCK: Well, it is thought that, through some genetic abnormality, these patients cannot manufacture ceruloplasmin. This particular patient we are discussing to-day had no ceruloplasmin, but I have seen classical Wilson's disease with a normal serum ceruloplasmin level, so that this cannot be the whole story.

Professor KING: Did anyone ever try to treat those with a low ceruloplasmin by giving them some?

Professor SHERLOCK: Yes, they have. But it is of no clinical benefit.

RESPONSE TO TREATMENT

Dr. MILNE: I think the big difference in response to treatment is that cases of pseudosclerosis, which usually occur in an older age-group, have always responded far better than this so-called juvenile type, such as the case to-day. One big difference in the pathology is that the juvenile types usually have cavitation of the basal ganglia, whereas the pseudosclerosis types only have a gliosis which is obviously much more reversible. I think in the future we shall be hearing of the treatment of asymptomatic sibs of cases of Wilson's disease—brothers and sisters of known cases who have been picked up by abnormal biochemical findings—long before they have developed any sign or symptom of the disease. They, I think, should be hopeful prospects for successful prophylaxis, just as in phenylketonuria you get a successful response only if you treat the disease long before it can be recognized otherwise than biochemically. In Wilson's disease, the biochemical investigation is so difficult that obviously it could only be applied to siblings of known cases.

Professor MCMICHAEL: Do you imply, Dr. Milne, that cases of pseudosclerosis also have this same copper abnormality?

Dr. MILNE: Yes, Sir.

Professor MCMICHAEL: And you think that it may well be a delayed form, or a slower or less acute form?

Dr. MILNE: I think that is the current neurological concept. Is that right, Dr. Pallis?

Dr. PALLIS: I am not at all sure what "pseudosclerosis" is, or whether in fact such an entity really exists, but I agree with Dr. Milne that mild cases of hepato-lenticular degeneration are seen in which the abnormality of copper metabolism has almost certainly antedated symptoms. This may occur in every case.

*Howell, J. S., *J. Path. Bact.*, 1959, **77**, 473.

I don't think there is really any fundamental incompatibility between the two observations (*a*) that she didn't improve clinically after treatment, and (*b*) that no copper was found in the basal ganglia. The copper that had been deposited there had probably damaged a number of the neurones irreversibly. Treatment had then removed much of the deposited copper, but of course hadn't resurrected the damaged cells.

SKELETAL ABNORMALITIES

Professor MCMICHAEL: Are there any further points from anybody? Dr. Rosenoer, from St. George's Hospital, have you any comments to make on this case?

Dr. V. M. ROSENOER: Yes. Dr. R. C. Michell and I have been investigating 10 cases of Wilson's disease seen at St. George's Hospital during the past six months. Finby and Bearn in the United States have demonstrated that in 20 cases of Wilson's disease a large proportion had skeletal abnormalities—osteomalacia, bone fragmentation, and osteoarthritis. In our 10 cases a very high proportion had abnormalities: 7 had osteochondritis of the spine, mainly in the mid-dorsal region; 4 had bone fragmentation at the articular margins, mainly in the wrists; 3 had typical osteochondritis dissecans, and 4 had osteoporosis: in only 1 of these was the osteoporosis very marked—a patient of Professor Sherlock at the Western Fever Hospital. All the patients had hypercalciuria.

When the patient we are discussing to-day died, we obtained a specimen of bone from her—the left knee-joint. We have a picture of this joint (Fig. 9) showing typical osteochondritis dissecans; a radiograph shows that the bone is involved as well as the cartilage. The histology is not yet available. The cartilage does not show any excess of copper, although the synovial membrane, which we studied ourselves, does show excess iron as demonstrated by Perl's stain. We are unable at present to explain these degenerative joint changes; we had expected that the bones would show an excess copper content, but these estimations are not yet completed.

IRON DEPOSITION

Professor MCMICHAEL: That is very interesting. I don't think we came round to the point of the iron deposition. Professor Sherlock was unwilling to accept the idea that this resulted from transfusion.

Professor SHERLOCK: Well, I know that once iron is in the body, it is there for ever, but our patient hadn't had any transfusions for two and a half years.

Dr. PEARSE: But she had a large amount of protein, off which you took the copper, just waiting for something else. If you had given her silver, it would have taken that up.

Dr. MILNE: Does not this potassium sulphide treatment also precipitate iron sulphide, which I should have thought was rather insoluble and would therefore prevent absorption of iron?

Professor SHERLOCK: I remember in a previous published conference* describing a patient with cirrhosis showing iron in the liver; that patient also had a large portal collateral circulation. Admittedly, it was a natural one, and this patient has an artificially produced shunt. It may be that an abnormality of iron metabolism is in some way associated with the presence of a collateral circulation.

Brit. med. J., 1959, **1**, 568.

RENAL FEATURES

Professor MCMICHAEL: Dr. Milne, would you comment on the aminoaciduria and other renal features of this case? There seems to be no explanatory renal histological change.

Dr. MILNE: Well, obviously the proximal tubular lesion is not gross. It has not been recognized by classical histology, and, unlike in the Fanconi syndrome, there is no obvious abnormality on micro-dissection. It is generally thought to be due to copper poisoning of proximal tubular function, and it does involve, pretty well specifically, substances thought to be excreted by the proximal tubule. For instance, there is increased excretion—i.e., diminished tubular reabsorption—of glucose, many amino-acids, phosphates—which presumably is the cause of the osteomalacic lesions reported, and uric acid—shown clinically by the low serum uric acid. Distal tubular function, such as concentrating power and renal acidification, was tested in this patient and found to be quite normal. The defect is very much a purely proximal tubular lesion. More specific defects of proximal tubular function, particularly in the tubular maximum secretory capacity of para-aminohippurate, are well marked in Wilson's disease, so that the lesion is very specific.

I was interested in Dr. Pearse's point about the nephrocalcinosis. Clinically, nephrocalcinosis is rarely seen in cases of aminoaciduria. In this respect the aminoacidurias contrast very markedly with renal tubular acidosis, where there is very commonly a nephrocalcinosis. It is usually thought that aminoacids chelate calcium and therefore prevent deposition of calcium in the kidneys. So I think Dr. Pearse's work is of great interest, and I trust he will report it in more detail.

Professor KING: If the poisoning of the enzyme systems which normally cause reabsorption of those substances Dr. Milne has talked about is the true explanation, then the withdrawal of excess copper should have operated to restore reabsorption.

Dr. MILNE: I think that is one thing that hasn't been well investigated—the response of renal function to treatment. But, so far as I know, certainly the generalized aminoaciduria—which is, I think, the most constant of the defects and seen in almost all cases—has not been described as clearing up with treatment. So that again you have to postulate that the enzymatic defect seems to be rather irreversible, which does correlate, I think, with the really very poor ultimate results of therapy on the basal ganglia and the liver.

Professor KING: But that doesn't correlate well with the supposition that it is simply a poisoning of an enzyme. In the presence of a chelating agent copper doesn't poison enzymes.

Dr. MILNE: I think in the same way the removal of iron in haemochromatosis, although it improves the patient, does not leave that patient normal. It is very much more subtle than merely the presence of a substance actually inhibiting tissue enzymes.

Professor MCMICHAEL: Well, I think we must leave it there.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

Drug Treatment of Disease

CARDIAC ARRHYTHMIAS

BY

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Abnormal rhythms of the heart are commonly causes of heart failure and syncope, and paroxysms of arrhythmia may, over years, cause recurring distress and disability. The drug treatment of such disorders is of importance, since there are rarely any other direct means of preventing attacks or bringing them to an end.

In the treatment of fast abnormal rhythms the three drugs frequently in use are digitalis, quinidine, and procaine amide, while prostigmine is occasionally required. When arrhythmias are slow, as in various forms of heart block, ephedrine, adrenaline, isoprenaline, and atropine are employed. The action of these principal groups of drugs and their administration will now be considered. Subsequently an account will be given of some drugs which aim to redress electrolyte balance such as potassium chloride and sodium lactate, which may play important parts in the control of cardiac arrhythmia.

DIGITALIS

While it has been proved that digitalis in the usual dosage has no influence on the healthy human heart or circulation, it acts on the auricles in heart disease by increasing the refractory period and through the vagus by slowing formation of impulses at the sino-auricular node. It also slows conduction through the bundle of His and the auriculo-ventricular node. Moreover, digitalis improves the power of the failing ventricular muscle and increases cardiac efficiency. Its essential use is in the treatment of heart failure, and it is of special value when this is associated with auricular fibrillation due to rheumatic heart disease.

Auricular Fibrillation

In this condition the heart rate is frequently high and there is a wastage of myocardial power because some contractions are too feeble to assist the circulation, as shown by the weak radial pulse. When the heart is slowed the ventricular filling improves and each contraction contributes to the circulation. Through this effect and its power of increasing the force of myocardial contraction, digitalis relieves the distress of heart failure, slows the rate of the heart, and promotes diuresis, processes which are expressed by the term "digitalization."

The total quantity of digitalis needed to achieve this state will vary according to the speed with which control is to be secured. The digitalizing dose needed for a patient weighing 11 stone (70 kg.) is about 22 gr. (1.4 g.) of the tablet digitalis folia, or about 3–4 mg. of digoxin ("lanoxin"). In severe heart failure treatment should start with an intramuscular injection of lanoxin 0.5 mg. or "cedilanid" 0.4–0.8 mg. Treatment may then be continued orally.

If large doses are given initially a smaller total amount is needed because there is less time for excretion. In general, a good plan is to use tablets of digitalis folia gr. 1 (65 mg.), giving on the first day 6 to 9 gr. (0.4 to 0.6 g.), on the second day 4 to 6 gr. (0.26 to 0.4 g.), and thereafter 3 gr. daily (0.2 g.), depending on the response in terms of heart rate and the clinical state. When it is judged that full benefit has been secured, or when the first indication of toxicity occurs, a lower dose, such as gr. 1 (65 mg.) twice daily, should be given. The ultimate maintenance dose will be that needed to keep the heart rate at about 60–70 per minute.

Digitalis is not expected to convert auricular fibrillation to normal rhythm, though the restoration which sometimes occurs may appear to be due to the action of the drug. The term digitalization also implies that the gradual accumulation which takes place in the body does not reach the degree needed to produce the evidences of intoxication, which are (i) coupled rhythm, (ii) nausea and vomiting, and sometimes (iii) an abnormally slow rate of the heart.

Auricular Flutter

Digitalis given in substantial dosage is the most effective means of restoring normal rhythm when auricular flutter exists. The quantity then needed may be above that already described for digitalization. Treatment is continued until auricular fibrillation is induced; if at this stage the administration is stopped, sinus rhythm returns in about two-thirds of cases. If flutter resists this treatment, digitalis may be continued in doses needed to control the rate, perhaps as 4:1 flutter, while at the same time quinidine is given in increasing dosage (see below) until normal rhythm is restored. As the conversion of auricular fibrillation or flutter to normal rhythm requires close clinical and cardiographic control, these procedures should generally be undertaken in hospital, unless special facilities are available elsewhere. There are a few patients in whom flutter resists conversion, or in whom flutter persistently recurs. In them, long-term control by digitalis has to be used.

Auricular Paroxysmal Tachycardia

If pressure on the carotid sinus has failed to restore normal rhythm, and if an injection of prostigmine 0.5–1 mg. subcutaneously or intramuscularly has also been unsuccessful, digitalization should be accomplished either by cedilanid 0.5 mg. as a slow intravenous injection or by lanoxin 0.5 mg. intramuscularly. Oral dosage will follow, and after digitalization has been achieved a daily maintenance dose should be continued for three months. Sometimes neither prostigmine nor digitalis converts the rhythm to normal, but either may render the patient sensitive to carotid-sinus pressure, so that this manœuvre, previously unavailing, becomes effective.

QUINIDINE

This isomer of quinine has for more than 40 years been recognized as having a favourable effect on the rhythm of the heart. It lengthens the refractory period of the myocardium by its influence on the vagus, the myocardium, and the conducting system. Its main clinical uses are in the conversion of auricular fibrillation to normal rhythm, in the control of extrasystolic rhythm, in the conversion of auricular flutter to normal rhythm, and in the treatment of ventricular paroxysmal tachycardia.

Auricular Fibrillation

It has been seen that digitalis cannot be expected to do more than control the rate of this arrhythmia. If the irregularity is of recent onset and not due to acute or advanced degenerative lesions of the myocardium, the physician may decide to attempt restoration to normal rhythm. For this purpose administration of quinidine is necessary. Quinidine sulphate gr. 5 (0.32 g.) is given orally at two-hourly intervals for six doses. The same dose should be given for the next two days. This will bring the plasma level to about 6–8 mg. per litre. If abnormal rhythm persists, the dosage may be increased a little but only under cardiographic control. Thus if the QRS interval increases to 0.14 sec., or if multifocal extrasystoles appear, or if vomiting or diarrhoea occurs, administration must be stopped. If the heart rate rises to 130 or more during treatment, administration should be discontinued pending control by digitalis; another trial by quinidine should then be made. Once normal rhythm has been restored and proved cardiographically, the dose of quinidine is reduced to gr. 5 (0.32 g.) three times daily and continued for a month. If relapse to fibrillation occurs readily and repeatedly after conversion, the attempt to restore normal rhythm should be abandoned.

Auricular Flutter

It has been said that digitalis is the treatment of choice for the correction of this arrhythmia, but if it is unavailing quinidine may be successful either alone or in conjunction with digitalis. If used alone, it should be given by the procedure described above for conversion of auricular fibrillation. Sometimes quinidine may be needed to supplement digitalis in the treatment of flutter. Thus, if digitalis fails to convert flutter beyond the stage of fibrillation, its administration is continued while quinidine is given orally gr. 5 (0.32 g.) thrice daily. Once normal rhythm has been restored, a maintenance dose of digitalis folia gr. 1 (65 mg.) t.d.s. or quinidine sulphate gr. 5 (0.32 g.) t.d.s. should be given for a month.

Extrasystoles

Very often no cause can be found for these arrhythmias, whether they arise from the auricle or the ventricle or in nodal tissues. If a cause such as focal sepsis is found, appropriate preventive action should be taken. Sometimes ectopic beats denote ischaemic or other heart disease, heart failure, thyrotoxicosis, or chronic alcoholism, and the treatment of the irregularity will then be that of the underlying disorder. In the absence of a causal disease requiring treatment, extrasystoles should be treated medicinally only if they weigh in the patient's mind or disturb sleep at night. In such events, quinidine gr. 3–5 (0.2–0.32 g.) thrice daily is the drug of choice, or procaine amide or ("pronestyl") 250 mg. four times a day may be tried. Sometimes a simple sedative such as amytal gr. ¼ (50 mg.) twice daily, is more effective. The arrhythmia may remain refractory to treatment.

Ventricular Paroxysmal Tachycardia

This arrhythmia is often self-limiting, the attacks being so brief that they are over before treatment can be administered. Attacks that last several hours or days may follow cardiac infarction, and these may be very difficult to correct more than temporarily. For such paroxysms quinidine sulphate is the treatment of choice, and is given orally in doses of 5 gr. (0.32 g.) two-hourly for eight doses. If this results in a return of normal rhythm, gr. 5 (0.32 g.) should be given thrice daily for a week or ten days, the dose being then tapered and discontinued. The suppression of recurring brief bouts of ventricular tachycardia may often be achieved by quinidine sulphate gr. 5 (0.32 g.) three or four times daily. If quinidine treatment is not successful in arresting these arrhythmias, pronestyl should be administered as described below.

PROCAINE AMIDE

This substance, introduced into clinical medicine less than ten years ago, has gained some recognition as a safeguard during anaesthesia and as a medicament for the control of cardiac arrhythmia in day-to-day practice. It acts by increasing the refractory period of both the auricle and ventricle and it also depresses vagal activity. Given by injection during anaesthesia, it helps to maintain regular rhythm in subjects known to be liable to arrhythmia, such as ventricular tachycardia, or the multiple extrasystoles that may occur during cyclopropane anaesthesia.

Procaine amide is less likely than quinidine to banish extrasystoles, but it may be given orally in doses of 250 mg. every four hours for two or three days, whether the arrhythmia is auricular or ventricular. Certain toxic effects may be encountered. Gastro-intestinal disturbances such as anorexia and vomiting occur, chiefly with oral administration, and may or may not invalidate its use. The more serious side-effects on the circulation arise when it is given intravenously, and the chief risk is of hypotension. This usually occurs, and sometimes it induces alarming effects by worsening impending shock and causing angina.

Procaine amide is also given in attempts to abolish paroxysmal tachycardia, wherever the focus may be, though it is more likely to be effective in ventricular tachycardia. Bellet (1958) has analysed the results claimed from this treatment in four published reports comprising 279 cases in all. Ventricular tachycardia was brought to an end in 69%, ventricular extrasystoles in 91%, supraventricular tachycardia in 68%, auricular fibrillation in 7%, and flutter in 5%. On the other hand, there is no arrhythmia in which procaine amide is generally regarded as the treatment of choice, though some may prefer it to prostigmine in the treatment of auricular paroxysmal tachycardia. Procaine amide may also be given intramuscularly in the dose already mentioned; though the results may be less certain, toxic effects may thus be avoided.

PROSTIGMINE

If in auricular tachycardia carotid sinus pressure fails to bring the paroxysm to an end, the drug most likely to succeed is prostigmine. It is given subcutaneously in a dose of 0.5 mg. Constitutional upset may follow—notably nausea and vomiting—but sinus rhythm may simultaneously be restored.

POTASSIUM

There has been in recent years an increasing realization of the importance of potassium in the function of the myocardium and in the maintenance of normal rhythm. If this electrolyte exists in excessive amount in the blood stream it may cause cardiac arrest. Conversely, deficiency of potassium increases the effect of digitalis on the heart. Moreover, it is a cause of arrhythmia and may explain the failure of digitalis to benefit the rhythm or the clinical state in some patients with heart failure. In these circumstances the heart still has a fast irregular rhythm but the patient is actually receiving more digitalis than is required, and perhaps more than he should. Estimation of the blood electrolytes may reveal deficiency of potassium. If then potassium chloride is given orally in doses of 5 g. daily, ventricular ectopic beats may disappear while the heart rate slows and the signs of heart failure abate. If the need is more urgent, potassium may be given intravenously as Darrow's solution. Should the potassium level in the blood be too great (a possible cause of rapid nodal rhythm), an infusion of one-sixth molar sodium lactate may correct this and often the associated arrhythmia.

It should be remembered that low-sodium diets and the long-continued use of mercurial diuretics may result in harmful disturbance of electrolyte balance. In this event less restriction of the sodium and correction of the potassium imbalance commonly brings swift improvement.

Slow Cardiac Arrhythmias

It has been seen that fast abnormal rhythms of the heart cause distress which is partly haemodynamic and partly emotional, and which is often incapacitating in varying degree. They may be responsible for heart failure and for syncopal attacks. Abnormally slow rhythms have equally harmful effects on the circulation and commonly lead to cerebral anoxia and syncope. The effects are thus in some ways similar to those of the fast arrhythmias but the problems of treatment are entirely dissimilar. The principal causes of bradycardia are depression of function or disease of the A.–V. node or bundle of His, depression of the S.–A. node or block between this node and the auricles, and overaction of the carotid-sinus mechanism. In any of these slow arrhythmias it is likely that overaction of the vagus contributes to the disorder. The general therapeutic indication is then for drugs which increase the excitability of the heart and its conducting tissue and in less degree those which impair or abolish vagal activity.

EPHEDRINE

This substance, given in doses of gr. ½–1 (32–65 mg.) thrice daily, is the most effective means of increasing the rate of the heart and for lessening the frequency of fainting or syncope. It acts by sympathetic stimulation and by improving the conductivity of the bundle of His. It is thus effective in accelerating the rhythm in partial heart block and in sino-auricular block. Even in complete A.–V. block, when the rhythm depends on the ventricles, ephedrine (like exercise or fever) increases the rate by a few beats a minute.

ADRENALINE

If the patient has Stokes–Adams attacks due to intermittent cardiac arrest or excessive slowing, injections of adrenaline are required. This is given as adrenaline hydrochloride, 5 minims (0.3 ml.) subcutaneously every two hours. A loaded syringe is kept in readiness for immediate treatment should more prolonged ventricular asystole occur. Sometimes Stokes–Adams attacks are associated with ventricular tachycardia. In such cases adrenaline is inadvisable, and quinidine and procaine amide are also contraindicated. The treatment advised is the sublingual administration of isoprenaline 20 mg.

ATROPINE

Through its action in depressing vagal activity atropine sulphate might be expected to increase the rate of the heart, but vagal activity is poor below the A.–V. node. Actually it is of little avail when heart block is present unless in conjunction with adrenaline. Atropine sulphate gr. 1/50 (1.3 mg.) given subcutaneously twice daily is always worth while giving when adrenaline alone does not produce the results expected.

SODIUM LACTATE

Normal solutions of sodium lactate given by intravenous drip have a powerful effect in stimulating the heart and increasing its rate. This effect may be particularly striking when bradycardia is associated with hyperkalaemia and in the Stokes–Adams syndrome. It is believed to act by favouring alkalosis, by the lowering of serum potassium, and perhaps by the direct effect of the lactate ion and an influence on the vagus. As the action of sodium lactate is entirely different from that of other drugs that excite the heart, it may reinforce their effect or even be advantageous when other remedies are without effect.

CORTICOTROPHIN (A.C.T.H.)

The successful use of this steroid in isolated cases of Stokes–Adams syndrome has been reported by Litchfield *et al.*

REFERENCES

Bellet, S. (1958). *Amer. Heart J.*, **56**, 479.
Litchfield, J. W., Manley, K. A., and Pollak, A. (1958). *Lancet*, **1**, 935.

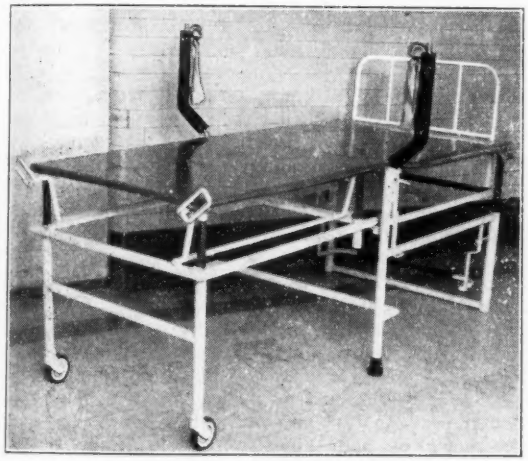
"In the sphere of medicine and in the sense of something of value and based on experience that is handed down by word of mouth from senior to junior, tradition can teach that the very apprehensive patient is a 'bad surgical risk' and likely to make an eventful recovery from any operation, if indeed he does not succumb. This is equally true of the man who changes his religion on the night before a major surgical procedure, the man with piles of books, especially French novels, at each side of the bed, and the man who after a surgery is found reading his newspaper upside down. There is a well-founded tradition that intussusception babies are liable to burst after laparotomy, and that patients with red hair are prone to develop keloid scars." (The Cavendish Lecture, 1958, "On Tradition," by Sir Gordon Gordon-Taylor. *Proceedings of the West London Medico-Chirurgical Society, 1958.)*

New Appliances

A CONVENIENT OBSTETRIC BED

Mr. A. B. FLETCHER and Mr. G. D. MACDONALD, of the Engineering Department, Royal Victoria Infirmary, Newcastle upon Tyne, write: The obstetric bed described here has been evolved in an attempt to overcome the disadvantages of the models in current use while sacrificing none of their good points. The requirements of a good obstetric bed are: (1) It should be wide enough to ensure comfort for the patient during a prolonged labour. (2) It should be so designed that the patient can be placed rapidly and easily in the lithotomy position with a minimum of movement. Once in this position she should be readily accessible to both obstetrician and anaesthetist. (3) It should be so arranged that in an emergency a rapid head-down tilt can be assumed and the horizontal position just as easily restored. (4) There must be sufficient rigidity to allow of all obstetric manœuvres being carried out without the whole structure being too cumbersome for the nursing staff to move when necessary.

These aims have been achieved by designing a bed in two sections—a head end which supports the patient's body at all times, and a foot section which supports the legs during the first stage and which, when the lithotomy position has been assumed, can be telescoped under the head end.



An overall view of the bed, without mattress, is shown here. The head-piece of the bed is made to lift out and the lithotomy stirrups are designed to fit into the legs of the head section. To assume the lithotomy position the patient's legs are raised, the stirrups swung inwards, and the feet slung in position. To dispose of the lower end, the handles visible at the foot of the bed are rotated inwards, when the top of the foot section drops on to the main frame and the whole of this part of the bed can then be pushed under the head end. There is sufficient clearance between the two parts to permit the use of a split 4-in. (10-cm.) sorbo mattress.

The head of the bed is supported on two hydraulic jacks and is held in the horizontal position by two spring-loaded locking-pins. These pins are connected to a kicking-bar, so that, when this bar is kicked forward, the pins are withdrawn and the head of the bed drops smartly to an angle of 15 degrees. The shock of the fall is absorbed by the damping action of the jacks. To level the table again, it is necessary to lift the head end by hand, an easy matter, when the locking-pins will automatically re-engage and maintain the horizontal position.

(Continued at foot of next column)

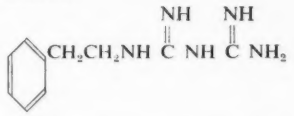
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Phenformin

" Dibotin " (Bayer).

Chemical Composition.—This is phenethyldiguanide, or N'-phenethylformamidinyliminourea hydrochloride. Its formula is as follows:



Pharmacology.—Phenformin is a recently introduced oral hypoglycaemic agent which will lower the concentration of glucose in the blood of most diabetics irrespective of the type of diabetes. The mechanism of its hypoglycaemic action, which must be different from that of the sulphonylureas, is unknown, but it may be due to increased anaerobic glycolysis resulting from reduction of oxidative phosphorylation.

Clinical Uses.—Phenformin is given two to four times daily with meals and may be useful in the treatment of:

(1) Patients with stable, insulin-dependent diabetes which began in adult life. Those uncontrolled by diet alone who have failed to respond satisfactorily, either initially or later, to a sulphonylurea and to whom the injection of insulin would present difficulties may be controlled by phenformin alone. In addition, those responsive to, but inadequately controlled by, a sulphonylurea may sometimes be treated satisfactorily by the addition of a small daily dose of phenformin.

(2) Other patients with insulin-dependent diabetes. An attempt should never be made to replace insulin entirely, and, though phenformin may reduce the insulin requirement, there appears to be little advantage in this combined therapy. As yet, there is insufficient evidence to substantiate the claim that phenformin facilitates the control with insulin of patients suffering from so-called " brittle diabetes."

Side-effects.—The clinical use of phenformin is seriously limited by the high incidence of gastro-intestinal side-effects—anorexia and nausea, and less often vomiting and diarrhoea—particularly when more than 150 mg. is given daily. These do not occur so frequently if the drug is given in small initial doses gradually increased. Nevertheless these side-effects occur in some patients given as little as 50 mg. daily.

The indications for phenformin in the treatment of diabetics, the over-all metabolic consequences of its continued administration, and its mode of hypoglycaemic action need to be more fully established. At present phenformin should be given only to patients carefully and regularly supervised at hospital clinics.

Available only to hospitals and diabetes clinics.

(Continued from preceding column)

The prototype of this bed was made in the engineering shop of the Royal Victoria Infirmary, Newcastle upon Tyne, and has been in use for some considerable time in the Princess Mary Maternity Hospital, Newcastle upon Tyne, where it has proved very satisfactory in practice.

Doctors who are interested in the construction of a bed to this design should write to the Department of Anaesthetics, Royal Victoria Infirmary, Newcastle upon Tyne, for detailed constructional data.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Mothers' Preference in Confinement

SIR,—Drs. I. Gordon and T. F. Elias-Jones (*Journal*, January 2, p. 52) found in their survey in Ilford that 80% of the mothers investigated preferred a home confinement. This is taken to conflict with evidence presented to the Cranbrook Committee that most women preferred to have their babies in hospital. (The committee also says that, in the opinion of nearly all its witnesses, "some women, perhaps between 10% and 20%, preferred to have their babies at home.") Specialist obstetricians and others are taken to task by Drs. Gordon and Elias-Jones for being unaware that "mothers *generally*" (my italics) prefer home confinement. Drs. Wauchob and Roberts (*Journal*, January 30, p. 349) have started a similar survey in Blackpool and appear to agree with the Ilford investigators.

Surely the conflict of evidence and opinion arises from the method used in these surveys? Both are restricted to mothers who have experienced both a home and a hospital confinement. This procedure, though superficially fair and reasonable, means that only a minority of women are consulted (336 out of 1,552 in Ilford); these form a sample which is by no means representative, and one should not generalize from their views. In both areas about three-quarters of all mothers are confined in hospital, and in Ilford at least "there is considerable medical, obstetrical, and social weeding out of those desiring hospital confinement." If a large majority of women seek hospital confinement, to an extent that many have to be turned away, this suggests that a majority of all mothers in these areas prefer hospital confinement.

We have examined birth records for the city of Aberdeen to see what kinds of mothers choose home confinement, and also to determine the bias produced when only those women are selected who have experienced both a home and a hospital confinement. The supply of maternity beds in Aberdeen is sufficiently large to permit the acceptance of all women who ask for a hospital booking. If a woman prefers to be confined at home, no pressure is put on her to book for hospital unless there are definite medical indications. Under these conditions of virtually unrestricted choice slightly less than 15% of Aberdeen mothers book for home confinement. Despite great improvements in housing, pressure on hospital beds has continued to increase steadily, and the present numbers can be accommodated only by curtailing the lying-in period. At periods of exceptional pressure we have occasionally asked a normal multipara with a good home to accept a domiciliary booking. Nearly all of these mothers expressed disappointment and some resentment. A few went so far as to persuade their husbands to complain to the Board of Management.

What kinds of mothers have their babies at home? The percentage in each parity booked in Aberdeen during the years 1957–8 for a domiciliary confinement is shown in the Table in the next column.

Parity	*Percentage Booked*
First	1.7%
Second	8.9%
Third	21.1%
Fourth	31.1%
Fifth	32.3%
Sixth and later	35.3%

Our general experience confirms that domiciliary confinement is most often the choice of women for whom a hospital confinement would mean abandoning *several* children to the care of the husband, relatives, or strangers. When there are only one or two children, arrangements which appear satisfactory to the mother can usually be made, and she then usually chooses to go to hospital. If questioned directly, the mothers of large families often give the answer most commonly given in the Ilford survey, that they prefer to be with their husbands and children. But this response frequently seems to be conditioned by domestic responsibilities and difficulties, and by no means necessarily represents a free expression of personal desires. The second most common response in Ilford was "Easier to rest or relax at home." In our view, this usually means that the mother is more at ease if she can keep an eye on things personally, however much she would like a rest away from domestic cares.

The third commonest response in Ilford was "individual attention at home; not just another case." It is by no means necessary for mothers in hospital to be treated as "cases"; good medical and nursing care, whether at home or in hospital, recognizes the importance of the individual.

It is undeniable that some women genuinely enjoy having their babies at home, but any generalization has to be reconciled with figures such as those given above. The bias towards high parities means that domiciliary confinement is most common among women in the poorer social classes. In our experience, mothers with the best housing and the greatest financial resources mostly prefer to go to hospital.

Among 3,105 mothers confined during 1958 in Aberdeen, 1,077 were primiparae. Out of 1,938 multiparae, only 403 had had experience of delivery both at home and in hospital. Most of these had a confinement at home after one or more confinements in hospital; the reverse order was much less common and was usually influenced by medical or obstetrical considerations. Analysis has shown these 403 women with experience of both kinds were considerably biased towards the older ages, higher parities and lower social classes. 261 of them had had their last baby at home.

Problems of sampling aside, direct questioning is by no means the most reliable method of ascertaining the preferences of women. It is not easy to formulate a question which does not in itself suggest the "right" answer. Even if the wording is beyond criticism, much depends on the attitude (or the assumed attitude) of the questioner. Doctors and health visitors are liable to be associated in the public mind with one policy or another. (Those in Ilford seem to favour home confinement, and this is presumably realized by mothers in Ilford.) Even if the right question is put by a completely neutral questioner, the answer obtained may reflect the mother's duties, responsibilities and fears at least as much as her own personal desires. In such circumstances the mother's behaviour is perhaps the most reliable guide to her feelings. It seems to be generally true that if an efficient, humane, and reasonably convenient hospital service is available, most women will use it unless their domestic responsibilities are so heavy that they cannot easily be delegated. We see no reason to doubt the

witnesses who told the Cranbrook Committee that there was in most areas an unsatisfied demand for hospital confinement. Since applicants are being turned away, this is apparently true even in Ilford.—I am, etc.,

Aberdeen. DUGALD BAIRD.

Drugs for the Menopause

SIR,—Professor T. N. A. Jeffcoate in his excellent article on "Drugs for Menopausal Symptoms" (*Journal*, January 30, p. 340) rightly states the need for caution, particularly in the administration of hormones. Nevertheless it is doubtful whether it is wise for anyone to make a dogmatic pronouncement concerning a subject such as the menopause, about which there is so little reliable information.

Unquestionably many of the symptoms formerly attributed to the menopause are attributable rather to the general process of ageing. To assume, however, that all women who complain of hot flushes are necessarily neurotic is not borne out by the facts. A sense of relief and well-being that can be afforded by minimal amounts of hormone has been borne out by the experience of many patients. The menopausal woman is in a very different condition from the adolescent. If she demands relief from the medical profession, who are we to refuse it?—I am, etc.,

London, W.1. JOSEPHINE BARNES.

SIR,—In his conclusion to his very interesting and informative article (*Journal*, January 30, p. 340) Professor T. N. A. Jeffcoate seems to take a very cavalier view of the troubles of the climacteric as of those of adolescence, and one wonders whether he has ever had to deal with them as a general practitioner. They can be very time-consuming, and in the case of menopausal symptoms so much can be accomplished by giving carefully regulated doses (0.01 mg.) of ethinyloestradiol for limited periods, with intervals of at least a month in between. Speaking as a general practitioner of many years' experience, the only time that phenobarbitone seems to be of real benefit is when there is a coincidental high blood-pressure, or when it is a case of true hypertension *per se*, the symptoms of which may closely simulate some of those of the menopause. Hence it is very important to take the blood-pressure, instead of readily assuming that the symptoms are menopausal. Of course, both factors may be operating.

It is surely right to assume that a gradual decline in the powers of the ovary is a cause of menopausal symptoms before actual amenorrhoea occurs. One sees this so frequently in practice that it is difficult to reach any other conclusion, and I am sure it is as right to say so, as it is to say that menopausal symptoms persist, or do not come on, until a matter of years after amenorrhoea has been established. Again, to think that a mere reduction of calorie-intake (much as one has always liked to think it) will of necessity reduce obesity in middle-aged women is to fly in the face of current and authoritative evidence, slim figures and the whole gamut of sex-appeal not withstanding.

Finally, does it really matter whether we say symptoms are due to the "menopause" or to the "climacteric"? As long as we all know what we are talking about, is such verbal hair-splitting really of any consequence?—I am, etc.,

Bath. G. L. DAVIES.

SIR,—The article by Professor T. N. A. Jeffcoate (*Journal*, January 30, p. 340) on "Drugs for Menopausal Symptoms" must have come as a considerable disappointment to many of your readers. The trials and tribulations of the menopausal patient can hardly be dismissed as being usually "traced to environmental causes," and to state that "except in a minority of carefully selected cases, there is little more justification for giving drugs (including hormones) for the flushes and tantrums of the climacteric than there is for the blushes and waywardness of adolescence" is surely to state the problem in too simple terms.

These psychosomatic disturbances are still imperfectly understood. Their chemical and/or glandular foundations are as yet ill defined, though the late Dr. Joan Malleson was working up to the time of her death on lines which may well lead to their elucidation. Every doctor knows that there are many women who need no help at all. Many need only reassurance and mild sedation. But in many cases the fact that patients have been given some insight into the cause of their instability and distress makes it no easier for them to handle themselves. These women need much wisdom and sympathy. It frequently takes considerable time to discover the most appropriate sedative or the exact hormonal dosage for the individual case. This latter point has been gone into in some detail by Professor Jeffcoate, but throughout the article there is an emphasis on the relative insignificance of the disturbances of the menopause. This gives a false picture of the seriousness of the troubles and of their social and emotional repercussions.—I am, etc.,

London, S.W.10. A. E. BERYL HARDING.

Postponement of Menstruation

SIR,—In the *Journal* of February 13 (p. 498) I read, with interest, Mr. G. T. Smedley's factual letter relating to postponement of menstruation. May I make a plea for reducing to a minimum the use of "hormone" therapy in general for the postponement of menstruation for the convenience of the patient? We still know too little about the long-term effects of hormone therapy upon the anterior pituitary, adrenal, ovary, and even upon the endometrium and the menstrual pattern to condone free and indiscriminate hormone therapy. There seems to be little objection to the once-in-a-lifetime indications, as the honeymoon or participation in Olympic sports, but it is very doubtful if its repeated use for holidays, sports, theatre, or dance engagements, or the week-end in the country can be justified. Let us not meddle with the menses.—I am, etc.,

Newcastle upon Tyne, 3. W. HUNTER.

Prolonged Survival of Bone-marrow Graft

SIR,—The fascinating case reported by Dr. J. O. W. Beilby and colleagues (*Journal*, January 9, p. 96) warrants some speculation additional to that given by the authors in their discussion.

Firstly, there was the dramatic improvement in the patient's clinical state almost immediately following the transfusion of bone-marrow. The same phenomenon was noted by Mathe *et al.*[1] who transfused with marrow subjects who had received whole-body irradiation in the lethal range of dose. Furthermore, the data of blood counts suggest that there was an immediate delivery of cells to the peripheral blood. This clinical improvement and the increased blood values are not likely to

have been due to any immediate output of cells by the limited number of cells transfused: more probably the procedure triggered the recovery of the recipient's own haemopoiesis. The time factor (which Beilby *et al.* adduce in another connexion) was such that spontaneous recovery was to be expected at this time. In neither this case nor any of those of Mathe *et al.* can one exclude the play of chance, but the repetition of the phenomenon inclines one to seek a causal connexion. Formerly, Jacobson,[2] and more recently Ellinger,[3] have attributed recovery from aplasia of the marrow consequent on irradiation to humoral action of experimental procedures. The invocation of a humoral mechanism, or some similar process, is certainly apt in the situations of Beilby *et al.* and Mathe *et al.*

Secondly, there was the persistence of a functioning graft of bone-marrow from a closely related donor, the sister, though a subsequently applied skin graft from the same donor was shed in, presumably, reasonably characteristic fashion.

In the discussion the authors talk of "tissue" antigens. If one follows the concepts of Medawar,[4] as we do, such T-antigens are responsible for transplantation immunity, such as the rejection of homografts of solid tissue like skin. However, the success of the graft of marrow was attributed by Beilby *et al.* to the loss from the patient's plasma of apparently natural "tissue" antibodies as a result of the recent excessive reaction to aminochlorambucil combined with anergy due to Hodgkin's disease and previous irradiation. "Tissue" antibodies are not part of Medawar's concept. He envisages rejection of homografts as due, predominantly, to a specific immune response of cellular rather than humoral nature. While humoral immune antibodies such as iso-haemagglutinins may be evoked by transplantation of homologous tissue we know of no such natural iso-antibody, though normal sera contain humoral antibodies reacting with cells of a different species. Although we have unpublished evidence from experiments in this laboratory (H. S. Micklem) that specific immune humoral iso-antibodies transferred passively into mice irradiated with 1,000 r of *x* rays will prevent the acceptance of grafts of bone-marrow injected as suspensions, we cannot, nevertheless, believe that such antibodies or natural antibodies could have played a part in the case under review.

The initial acceptance of the marrow graft we would interpret as a natural phenomenon facilitated by the physiological need in a patient with aplastic marrow. The persistence is more remarkable. According to the results of investigations, the output of red corpuscles by the graft was small but relatively constant for some four months, following which there was a very substantial increase—and this apparently in spite of the patient's ability to reject, presumably by the classical cellular response, a skin graft of the same donor. It could be postulated that ultimately the patient's immune cellular response to the donor's T-antigens had recovered adequately but that there was no concomitant recovery of the humoral response to the donor's H-antigens. There were, in fact, no demonstrable anti-D or anti-E antibodies. The specific failure of animals to respond to certain H-antigens following administration of large doses of the antimetabolite, 6-mercaptopurine, has been reported by Schwartz and Dameshek.[5] The persistence of this marrow graft, certainly as regards the erythron, could be, like the retention of transfused blood, dependent on the absence of a response to H-antigens with humoral antibody. That is to say, transplantation of the erythron and perhaps the entire marrow could obey laws special to it and somewhat different from those of homografts in general. Much of the admirable work of Gorer and his colleagues[6] in the transplantation of leukaemic cells of the mouse would favour this concept.—We are, etc.,

D. W. H. BARNES.
H. S. MICKLEM.
J. F. LOUTIT.

M.R.C. Radiobiological Research Unit,
Harwell, Berks.

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2 Jacobson, L. O., *Cancer Res.*, 1952, **12**, 315.
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6 Gorer, P. A., in *Advances in Cancer Research*, 1956, p. 149. Academic Press, New York.

Erythema Nodosum after Liver Extract

SIR,—I was interested to read the article by Dr. F.-D. C. Ford (*Journal*, February 6, p. 400). Some years ago I received one 2-ml. injection of "anahaemin" (erythropoietic fraction of liver) in the arm for anaemia. This was followed about a month later by cellulitis at the site of the injection. It did not respond to sulphadiazine or penicillin injections and was incised. A clear, serous fluid was obtained. A week or so later erythema nodosum developed on the front of both legs. "Benadryl" (diphenhydramine hydrochloride) was taken with no effect. Investigations for tuberculosis produced negative results. Sulphonamides taken on previous occasions had never produced erythema nodosum, and penicillin taken at a later date produced no reaction, so it was decided that it was an allergic response to the anahaemin.—I am, etc.,

TESSIE PHILLIPS.

Department of Pathology,
The Leicester Royal Infirmary,
Leicester.

Cold Injury in the Newborn

SIR,—I cannot agree with the statement in your leading article (*Journal*, February 6, p. 408) that by far the most important cause of hypothermia in the newborn in the British Isles is accidental exposure to cold. I have only made a small number of necropsies on babies whose death was ascribed to the "cold syndrome"; in every case that diagnosis was wrong. Cold injury should be a diagnosis of exclusion. I prefer to regard it as one manifestation of the "collapse reaction."

The most important cause of the collapse reaction is an infection to which the patient is unable to respond normally; it occurs at all ages. I have often been told that a gross inflammatory lesion revealed at necropsy could not have been there during life because the temperature was normal or low. The blood picture of the collapse reaction to infection is characteristic, but the observer must be experienced. The white-cell count is not raised (it should not be called "normal"), eosinophil and basophil polymorphs are absent, there is a gross shift to the left of the neutrophil series, and a

lymphopenia. This blood picture may give warning of impending death before that is apparent clinically. If treatment is successful the white-cell count begins to rise and the shift to the left to decrease, i.e., the findings most expected with an acute infection. If improvement is maintained a lymphocytosis develops; this is the haematological finding that accompanies obvious clinical improvement. Later the white cells become normal in number and quality.

Bronchopneumonia has been the common finding in the babies I have examined who were thought to have died of the "cold syndrome." To arrive at an accurate diagnosis in the newborn far more work must be done than is usually necessary in a necropsy on an older subject. Even then it must be quite easy for us to overlook osteomyelitis and other acute inflammatory conditions. Problems in acute inflammation are very difficult both ways in the newborn. Easy as they are to miss, their significance when found is not always clear, e.g., what is the meaning of umbilical sepsis, with masses of staphylococci, in a baby dying of asphyxia due to hyaline membrane without pneumonia?

If low-reading thermometers come into general use it is to be hoped that all using them will realize that there are more dangerous causes of a collapse reaction than cold injury.—I am, etc.,

Derbyshire Royal Infirmary, Derby. G. R. OSBORN.

Pigmentation of Jejunal Muscle

SIR,—Dr. Pamela M. Fullerton (*Journal*, January 23, p. 249) has found that the development of brown pigmentation of the jejunum is associated with abnormalities of the gastro-intestinal tract. We have recently observed a similar condition in dogs which had survived more than one year after operations which altered their alimentary function.

The first dog was killed one year after total gastrectomy. The second lived fourteen months after oesophagoduodenostomy (the stomach being left, with its vagal nerve supply intact, as a blind pouch draining into the duodenum). The third dog had a coeliac ganglionectomy and vagotomy performed six years previously. All the animals were severely underweight and had intestinal hurry and steatorrhoea. In each dog the whole of the small intestine was brown in colour and a pigment with the characteristic staining and other properties of lipofuscin was present at histological examination. Dogs which were killed within one year of total gastrectomy did not have discoloration of the bowel. It would appear that, in dogs, disordered function of the bowel must be present for at least one year before the pigment is deposited.

It is of interest to note that, as long ago as 1932, Mann and Graham[1] of the Mayo Clinic observed brown pigmentation of the intestine in dogs which had undergone total gastrectomy.

We wish to thank Dr. L. Golberg and Dr. J. P. Smith for their histological examination of the first two cases and Dr. M. A. Freedman for his permission to quote the third.

—We are, etc.,

I. D. A. JOHNSTON.
R. B. WELBOURN.

Department of Surgery, Queen's University, Belfast.

REFERENCE

[1] Mann, F. C., and Graham, A. S., *Ann. Surg.*, 1932, **95**, 455.

Dumping Syndrome

SIR,—In his letter (*Journal*, February 6, p. 420) Dr. T. L. Dormandy points out that the blood-sugar concentration and blood-glucose concentrations are not necessarily the same, and that our observations on the dumping syndrome (*Journal*, January 16, pp. 141 and 147) were based on estimations of the former. He suggests that "the curious difference between their patients' response to hypertonic glucose drinks and a mixed breakfast" might partly be due to the presence of non-glucose sugars in the blood, and goes on to imply that the presence of such sugars in the blood may invalidate the correlation we found between the size of the fall in plasma volume (not, as Dr. Dormandy says, "blood volume") and the rate of rise of the blood-sugar concentration.

Regarding the "curious difference" referred to by Dr. Dormandy, we found, in patients with the dumping syndrome, no difference between their response to the ingestion of hypertonic glucose and that to a meal, except for a better quantitative response to insulin administration before a meal. The probable explanation for this was discussed in our second article. As regards the correlation between the fall in plasma-volume and the rate of rise of the blood-sugar concentration, this was observed in patients following the ingestion of a hypertonic solution of pure glucose. For these reasons we cannot believe that the well-established difference between blood-sugar and blood-glucose concentration can materially affect the significance of our observations. Concerning the technique we used to estimate the blood-sugar concentration, it may be stated that early in our work we discovered a hitherto unrecognized error in all techniques which estimate blood-reducing substances by the reduction of copper. Our results were obtained by a modification which eliminates this error. This aspect of the work is about to be reported in detail elsewhere.—We are, etc.,

L. P. LE QUESNE.
M. HOBSLEY.

The Middlesex Hospital, London, W.1.

An Intracardiac Pace-maker

SIR,—Your annotation (*Journal*, February 13, p. 491) rightly calls attention to the importance of an example of the clinical application of an intracardiac pace-maker by Furman and Schwedel.[1] In your discussion on this, however, you overlooked the communication by F. E. Weale,[2] of the Thoracic Surgical Research Unit at Guy's Hospital, in which he describes the use of an intracardiac electrode introduced via the jugular vein for cardiac resuscitation.—I am, etc.,

RUSSELL BROCK.

Guy's Hospital, London, S.E.1.

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[1] Furman, S., and Schwedel, J. B., *New Engl. J. Med.*, 1959, **261**, 943.
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Cardiac Arrest

SIR,—Perhaps it is not out of place to comment on the annotation on the treatment of cardiac arrest (*Journal*, February 6, p. 409). Cardiac arrest in the operating theatre is due to vagal inhibition or conditions leading to circulatory inefficiency of such degree that

myocardial anoxia causes cardiac still-stand or ventricular fibrillation. I include in this category cardiac arrest seen during cardiac surgery, hypothermia, or the careless use of thiopentone. Since the condition can be both anticipated and promptly dealt with, very many cases of cardiac arrest can be resuscitated by the use of the defibrillator, cardiac massage, or electrical pacemaker, without any post-operative neurological symptoms.

Cardiac arrest in the wards, however, in my experience, is of a very different causation—namely, cardiac failure due to pulmonary embolism or coronary occlusion of one of the major coronary arteries. Both these conditions are incompatible with life, and no known method exists which can restart such a heart *and keep it going*. The very few cases I can remember to have survived for a few days all showed irreversible cerebral damage. It might be better to give these facts due consideration, before mobilizing all available apparatus merely for the purpose of making a person die in three days instead of three minutes.—I am, etc.,

Boden, Sweden. ERIC A. FRAYWORTH.

SIR,—Your annotation on the treatment of cardiac arrest (*Journal*, February 6, p. 409) draws attention to the difficulties and delays that occur if this condition arises in situations removed from facilities for administering oxygen and performing thoracotomy. It may be of interest to draw attention to two methods of overcoming this difficulty in use in this city.

At Walton Hospital, Liverpool, the operating theatre technicians Messrs. J. Probert and W. Kehoe, with the aid of the hospital engineering department, have built resuscitation trolleys which are kept in the hospital admission room and in the operating theatres. These provide facilities for endotracheal intubation, suction, and bronchoscopy. In addition they carry an autoclaved drum containing the necessities for thoracotomy such as scalpel, rib-spreader, and scissors. These trolleys are carefully maintained, the oxygen cylinders and equipment being checked daily, and are easily and quickly moved to any part of the hospital. Their use has led to prompt successful treatment of many cases of respiratory and cardiac failure both on arrival in the hospital and in the wards.

In Liverpool Royal Infirmary, arrangements are being made to provide a locked cupboard containing the essentials for thoracotomy and resuscitation in the corridor between every two adjacent wards. The key of this cupboard will be kept in a glass-fronted case beside the cupboard. When required, the glass is broken, the cupboard unlocked, and the instruments are then immediately available. This equipment will also be regularly maintained and checked.

If the above or similar facilities were provided in all hospitals, the delay in starting the appropriate treatment for cardiac arrest—namely, oxygen administration and cardiac massage—would be much reduced. During the minimal unavoidable waiting period, however, the simple measures suggested in the annotation could be carried out.—I am, etc.,

Department of Anaesthesia, University of Liverpool. T. H. L. BRYSON.

SIR,—Your annotation on the treatment of cardiac arrest (*Journal*, February 6, p. 409) contains several recommendations which are of doubtful value and which, I feel, call for comment.

The suggestion that the electrocardiogram is important in the management of a patient with cardiac arrest is not only fallacious but dangerous. The first essential is to maintain adequate cerebral perfusion, which calls for cardiac massage. Correction of the underlying arrhythmia can be undertaken subsequently. If the heart is exposed for the massage, the nature of the arrhythmia will be obvious on inspection. The electrocardiogram is therefore unnecessary and time wasted to obtain it has, on several occasions in the past, been a reason for proper treatment being instituted too late to save the patient.

Admittedly, steps to commence cardiac massage when arrest occurs unexpectedly in the ward or at out-patients are not to be taken lightly; none the less, time spent thumping the chest or attempting to needle the heart is, again, liable to lead to dangerous delay in instituting the massage.

Finally, although it is true that external defibrillation is used, there are serious disadvantages to this, particularly on account of the large currents which have to be passed through the body, which may cause damage to tissues other than the heart. Similarly, although external pace-making can be performed, it is a very unpleasant procedure for the patient, and is unlikely to prove a satisfactory substitute for internal pace-making.—I am, etc.,

Guy's Hospital, London, S.E.1. D. C. DEUCHAR.

SIR,—Dr. R. S. Walton's contention (*Journal*, January 16, p. 155) that some cases of coronary thrombosis are fatal in virtue of damage to the conductive mechanism of the heart rather than to the heart muscle is supported by the following case.

On November 8, 1959, I was called to see a man of 69 who had mid-sternal pain. When I saw him at 3.30 p.m. he told me that his pain had started at church four hours previously and that he had been brought home by car. As he lay in bed he did not appear to be very ill, and his pulse was regular and of good volume. Suddenly he said, "Oh, doctor, I do feel bad," and lay back, apparently dead. Breathing had ceased; the pulse could not be felt nor the heart heard.

After about one minute I walked into the next room to inform the family that he had died. Returning to the bedroom with his son, I decided to attempt artificial respiration—supposing that it might be possible to create a feeble cerebral circulation by repeated pressure over the sternum and that the damage to the heart might be merely a reversible defect in its conductive mechanism. After about one further minute, during which I pressed on his sternum several times, the patient started to breathe again and his pulse again beat strongly. During the next hour his condition varied, but he did not regain consciousness, and I therefore asked Dr. R. G. Gibbs to see him. Auricular fibrillation was occurring and an electrocardiogram showed a posterior infarction.

We thought that the patient's failure to regain consciousness was due to cerebral anoxia and he was thereupon admitted to Lowestoft Hospital, where he remained unconscious for about 24 hours. Thereafter he made an uninterrupted recovery, and when I saw him recently he was ambulant and seemed none the worse for his misadventure. He was taking digitalis and chlorothiazide and his pulse was normal in rate and rhythm. Mentally he had returned to normal, except that he had complete retrograde amnesia for the events of November 8 for four hours previous to his loss of consciousness.

—I am, etc.,

Lowestoft. N. B. EASTWOOD.

Oculogyric Crises with Phenothiazine Derivatives

SIR,—The increasingly frequent use of phenothiazine derivatives in a wide variety of medical and psychiatric disorders has offered many opportunities for observing the toxic effects of these drugs, and on long-continued high dosage a clinical picture resembling Parkinsonism is now well recognized. A more severe dystonic affection was reported by Hare[1] following large doses of chlorpromazine, by Montgomery and Sutherland[2] after small dosage of perphenazine, and by Davies[3] following larger doses of the same drug. In each of the last two cases upward deviation of the eyes and marked neck retraction were prominent features. Recently we have had the opportunity independently of seeing two cases in which following acute overdosage of similar drugs, extreme oculogyric crises developed which rapidly recovered on withdrawal of the drug.

The first case was a 46-year-old woman who was well known to her practitioners as a psychoneurotic with a tendency to acute anxiety reactions to stress, of which there was an abundance in domestic affairs. Following a period of particular upheaval she was given a prescription for a "tranquillizing" drug, in this case "stelazine" (trifluoperazine), and was instructed to take two tablets three times a day. 5-mg. tablets were dispensed instead of 2-mg. tablets as had been intended. She took one dose of 10 mg. that night and two doses of 10 mg. the next morning and midday and fell to sleep during her work in the afternoon. She decided to return home, and on the bus her head began to be drawn backwards uncontrollably. Within 20 minutes she felt her eyes were forced upwards, at first intermittently, but they then became fixed in extreme upward deviation under the lids, the neck being retracted. She was quite unable to depress the eyes. Seen by her practitioner, who recognized this as an oculogyric crisis, she was instructed to take no more of the drug, and amphetamine sulphate was given. About eight hours later she was able to depress the eyes with great effort, but they returned to upward fixation immediately. There were no signs of extrapyramidal disturbance in any other part of the body. The following morning, 18 hours after onset, she had recovered full control of ocular movement but was extremely reluctant to look upwards for fear of reproducing the symptoms. Her recovery since then has been uneventful except for a return to her previous state of constant agitation.

The second patient was a 31-year-old woman, with four children, who, as a result of severe marital discord, had over a five-year period become increasingly depressed and irritable and was subject to frequent outbursts of hysterical behaviour with or without provocation. She had been treated for three months with perphenazine ("fentazin"), 4 mg. three times a day. At 4 p.m. on the day before admission to hospital and following a domestic upheaval she had taken 40 mg. of perphenazine in one dose with suicidal intent. There were no immediate effects and she slept soundly that night, but on waking suffered diplopia and vertigo. At 1 p.m., i.e., 21 hours after the large dose was taken, her head began to be pulled backwards involuntarily, and her eyes deviated upwards. Five hours later she was admitted to hospital, where the head was found to be retracted and pulled to the right and fixed in that position. Apart from slight tremor of the face there were no other neurological signs. On command she was able temporarily to depress the eyes, but they subsequently returned to upward deviation. She did not experience any of the ruminative obsessional thoughts which occur frequently during the oculogyric crises of post-encephalitic Parkinsonism. The condition began to subside about eight hours from the onset, she slept normally, and the next day was normal apart from pain in the nape of the neck. Her progress since then has been uneventful, and for three months she has been free from depression or hysterical outbursts.

It appears, therefore, that two types of extrapyramidal disturbance may be seen during the use of this type of drug—a chronic state resembling Parkinsonism from prolonged high dosage, and an acute condition characterized by long-lasting oculogyric crises accompanied by dystonic contractions of neck muscles. It seems that the latter picture is seen as a result of acute overdosage as in the cases described above, and by Hare[1] and Davies,[3] or as evidence of personal idiosyncrasy to the drug as in the case of Montgomery and Sutherland.[2] In either event prompt withdrawal results in rapid recovery. It is most important that practitioners should be aware both of the syndrome and of its treatment, particularly as its features are so bizarre that when it is a psychoneurotic or hysterical patient who is receiving the drug the symptoms may easily be regarded as merely another hysterical manifestation.

We wish to thank Dr. H. Maclean and Dr. J. W. Brown who referred these two cases.

—We are, etc.,

EDWIN R. BICKERSTAFF.

The Midland Centre for Neurosurgery, Birmingham.

E. JACOBY.

Highcroft Hospital, Birmingham.

REFERENCES

1 Hare, E. H., *Brit. med. J.*, 1958, **1**, 1462.
2 Montgomery, R. D., and Sutherland, V. L., ibid., 1959, **1**, 215.
3 Davies, T. S., ibid., 1959, **1**, 368.

New Drugs for Depression

SIR,—There is at the moment much interest in the use of the monoamine oxidase inhibitor type of drug in the treatment of depression, with particular reference to the possibility of E.C.T. being avoided.

I have not found that these compounds are significantly superior to placebos or other "active" drugs in the treatment of depression. However, there is a type of patient who does well on E.C.T. and then relapses rapidly, within a few weeks or months. It would appear that the exhibition of a monoamine oxidase inhibitor is of real value at this therapeutic stage—that is, immediately following a course of E.C.T. Presumably there is little to choose amongst the different proprietary makes, and in order to simplify matters I decided on using phenelzine ("nardil").—I am, etc.,

M. JEFFREY.

City General Hospital, Sheffield, 5.

SIR,—I have read with great interest the letter by Drs. F. A. Bleaden and G. Czekanska (*Journal*, January 16, p. 200) on their experience with antidepressant drugs and electro-shock therapy.

The letter does not convey the full details of technique and no mention is made of the amount of thiopentone and suxamethonium used. Also, in Case 1, the patient was placed on phenelzine two days prior to the E.C.T. in question, and therefore had not presumably received more than 90 mg. of phenelzine. The second case, however, had been given excessive amounts of the drug: 45 mg. given thrice daily is three times the recommended dosage of this antidepressant. Atropine gr. 1/100 (0.65 mg.) given subcutaneously 30 minutes before treatment apparently has been routine. This, however, is not the best technique. The atropine is not given by the attending physician, and, where a number of patients are to be treated, wide disparity

in time is bound to occur. The most effective and convenient method is to include the atropine with the anaesthetic substance.

A relative increase in blood pressure and heart rate occurs after E.C.T. The carotid and aortic depressor mechanisms via vagal pathways are stimulated, with resultant hypotension, bradycardia, and cardiac arrhythmia. Intravenous atropine prevents untoward effect of vagal stimulation. During the last year, we have used all of the known antidepressants in conjunction with electroshock and have found that we are effecting a 36% economy in the number of electric treatments required to produce recovery. The authors agree with the economy of E.C.T. which is now widely accepted.

Included in the many hundreds of patients treated by the combined method of antidepressants and electroshock therapy, we have had over 50 patients who have been taking phenelthiazine at the recommended dose of 15 mg. thrice daily, and at no time have experienced an adverse effect such as reported by Drs. Bleaden and Czekanska. The hydrazine compounds now in use as antidepressants yield very similar results in terms of clinical improvement, and in our experience no one of them has produced any adverse effect. In the light of my experience, I feel that the experience of these two doctors in a small series of cases may have proved alarming to them, but I feel that perhaps the technique of the treatment and not the adjunctive medication was the cause of the disturbing reaction. Undoubtedly, other experiences with these medications will be reported, and these two observers are to be commended on their reporting an unusual phenomenon even though the cause appears unknown.—I am, etc.,

EDWIN MCH. N. DUNLOP.

Fuller Memorial Sanatorium,
South Attleboro, Massachusetts.

New Treatment for Chronic Bronchitis

SIR,—Referring to the letter in the *Journal* of February 6 (p. 422) from Mr. B. D. Thornley, managing director of Benger Laboratories Limited, I feel that no satisfactory explanation of my poor clinical results and side-effects with "lomupren" and "lomudase" has yet been given. It should be possible for the manufacturers to answer the following points in precise detail, thereby dispelling finally any doubts which may remain.

(1) Mr. Thornley states that the dextran present in these powders is "material whose lack of toxicity when administered chronically by inhalation has been fully established in rats and guinea-pigs." It would be most helpful to know the published references to this work or any other published work on the chronic toxicity of inhaled dextran particles in man or animals, and if such work had been satisfactorily concluded *before* the product was launched on the open market.

(2) Mr. Thornley mentions "extensive clinical studies carried out before the product was made available." I should be most interested to have the reference to the publication of this work.

(3) I am sure all readers of the journal will be most interested to learn the results of the "closely controlled, objective and subjective investigations at a number of centres during the past year." The objective findings, particularly those regarding the effects of lomudase on the sputum, will be of the greatest interest in order to compare them with the findings of Dr. G. M. G. Barton in the same issue (p. 422), who demonstrated clearly that baking-soda was better than all these enzymes put together.

(4) Mr. Thornley continues, "There are, of course, innumerable references and much evidence as to the safety of dextran, particularly injection dextran *B.P.*" I would draw his attention to two papers by no less an authority than Kabat,[1,2] who has shown positively that dextran can be antigenic, and can produce skin sensitivity and the development of precipitins in man. Furthermore, as dextran is derived from sucrose by bacterial action, it must be difficult to exclude bacterial antigens from the final product. Kabat also pointed out that dextran is present as a contaminant of all commercial sugars, and also can be elaborated by micro-organisms in the gastrointestinal tract. He suggested that this might account for allergic reactions in individuals not previously injected with dextran.

My criticisms of Messrs. Benger's product were based upon the hard facts of clinical observations and objective measurements. To answer any criticism of this sort requires the publication of carefully designed clinical trials, and not a letter which appears to consist to a large extent in a re-statement of the claims which have already been made by Messrs. Benger's extremely efficient advertising campaign. Until the questions which have been posed here can be answered by published data with objective measurements on patients, I can see no reason to revise the views which I have already expressed regarding these products.—I am, etc.,

Derby Chest Clinic. H. MORROW BROWN.

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[1] Kabat, E. A., Turino, G. M., Tarrow, A. B., and Maurer, P. H., *J. clin. Invest.*, 1957, **36**, 1160.
[2] —— and Berg, D., *J. Immunol.*, 1953, **70**, 514.

Medico-legal Significance of the Fractured Skull

SIR,—The discussion in the *Journal* (January 23, p. 274, and February 13, p. 499) would have interested John Eric Erichsen, who, I believe, said that if a watch is dropped and the glass face is broken or fractured the inside may well be all right and still going normally, but if the glass is not damaged the inside might be wrecked.

On looking up Erichsen's most interesting chapter on "Injuries of the Head,"[1] the clinical experiences related therein have certainly lost none of their real significance for the doctor, or the factual evidence for the lawyer. It is an excellent example of the present-day value of one of the older books and the very great clinical experience incorporated in the writings. Also, Erichsen's careful analysis of the forces of impact, direct or indirect, and their dispersal on, about, or in the cranium is a most thoughtful practical application of the simple principle that if force X is applied and the skull is fractured it may well be a life-saving thing for the recipient.

It is certainly a fairly frequent observation now, when *x*-ray examination of the skull after head injury is almost routine, that a linear fracture of the skull is very common in infants and children and yet it is rather rare to detect anything more than minimal and transient cerebral disturbance, and a follow-up indicates usually no sequelae.—I am, etc.,

A. V. NEALE.

Department of Child Health,
University of Bristol.

REFERENCE

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Alcohol and Road Accidents

SIR,—With reference to the correspondence concerning alcohol and driving, it is beyond dispute that certain people on the roads are a danger by virtue of the consumption of alcohol, and it is also beyond dispute that the person who needs alcohol in order to drive is psychopathic and should not hold a driving licence. Does it not therefore follow that until such time as those who are dangerous can be restrained, all of us should be compelled to forgo the pleasure of alcohol, so that even a few lives could be saved ?

Does the punishment of an offender, after the accident, compensate in any way for the loss of a husband, wife, or child ?—I am, etc.,

A. A. CLAY.

Newport Pagnell, Bucks.

SIR,—I heartily support the views put forward by Dr. John H. Hughes in your issue of February 6 (p. 419) and his reference to the recently published Report of the B.M.A. Committee on the subject. On the other hand, Dr. Guy Rowarth (p. 419) states that " we can be certain that only a very small number of the far too numerous accidents on the road are caused by drink," and " if the country became teetotal to-morrow, there would be no significant alteration in the accident figures next week." Other statements follow which show not only ignorance of the subject but also strong prejudice, and which are inexcusable in a scientific journal. The B.M.A. Committee consists of a responsible body of experts who have studied the subject deeply and at length, and I do not think that their conclusions are likely to be upset. I hope that all B.M.A. members will send for this report and read it with an unprejudiced mind.—I am, etc.,

N. I. SPRIGGS.

Leicester.

SIR,—Why all this fuss about the motorist being frightened off alcohol before taking the wheel, for I suppose that this is the real reason for these proposed tests ? One might think that drivers were expected to undertake to become life-long abstainers so much protest is being made. When they have finished their driving they can indulge to their heart's content. There is so much resistance to the idea of these tests that one might conclude that true alcohol-addiction is quite common.

My teachers have told me that even a small amount of alcohol impairs one's alertness and powers of judgment, so greatly needed on the roads these days. Surely the facts are readily available from Sweden. Has this matter of tests for drivers decreased the accident rate or hasn't it ? Of course it is obvious that there are many factors apart from alcohol that may cause accidents, but this is one that we can do something about.—I am, etc.,

D. C. CLARK.

Penzance, Cornwall.

SIR,—All who have contributed to the recent correspondence on alcohol and road accidents agree that a number of accidents are caused by the impairment of judgment resulting from an excessive consumption of alcohol. Even those who describe the number as small would have difficulty in persuading the victims that it is insignificant. If the number can be reduced by the objective test proposed, no considerations of personal indulgence should be allowed to stand in the way.—I am, etc.,

V. J. HARTFIELD.

Buchanan Hospital
St. Leonards-on-Sea.

Reading the Number Plate

SIR,—The Regulations under the Road Traffic Act (S.I. No. 1664, 1955) require that the dimensions of the letters and numerals on a number plate shall be 3½ in. (8.9 cm.) high, the thickness of the individual strokes shall be ⅝ in. (1.6 cm.), and the total width of every letter and figure excepting 1 shall be 2½ in. (6.4 cm.). Normally, in the consulting-room, the distance of the subject from the test-card is 6 metres, and the distance at which the number plate is required to be read is 25 yards, or approximately 23 metres,* so that at 6 metres the examinee should be able to read letters of dimensions equal to one-quarter of those required by the regulations.

In reply to Dr. J. Shackleton Bailey's query (*Journal*, February 6, p. 429), I use a test-card representing both the square two-line plate and the single-line plate with letters and numbers ⅞ in. (2.2 cm.) high, 5/32 in. (0.4 cm.) thick, and ⅝ in. (1.6 cm.) wide. Experience shows that some letters are more difficult to identify than others, and my card is lettered accordingly.—I am, etc.,

S. CHAPLIN.

London, N.21.

* We regret that in Dr. Chaplin's previous letter (*Journal*, December 26, p. 1487) 25 yards was wrongly equated with 30 metres.—ED., *B.M.J.*

B.C.G. Vaccination

SIR,—Dr. E. F. James who, according to himself, has the unique distinction of being the only person to criticize the first report of the Tuberculosis Vaccines Clinical Trials Committee to the Medical Research Council[1] has now acknowledged (*Journal*, December 5, p. 1257) that the second report of the Committee[2] has established the protective effect of vaccination beyond reasonable doubt. He is, however, of opinion that the value of vaccination is limited in countries where tuberculosis is widespread. In support of this view he quotes the statement made by Dr. K. S. Sanjivi and myself (*Journal*, September 19, p. 500) that nearly 75% of Indian children are positive to 5 T.U. by the time they are 15 years old. Allowing for another 15% who would react to 10 or 100 T.U. he comes to the amazing conclusion that only 10% of these young people can hope to benefit from vaccination, and that in India " B.C.G. can only nibble at the edge of the huge problem." From this it is clear that Dr. James has no conception of the procedures in the mass vaccination programme. It has apparently not occurred to him that the W.H.O., Unicef, and the National Government of India would not spend their time, energy, and funds if only 10% of the young people stood to benefit from vaccination. He has failed to distinguish between vaccination in the mass campaign and that as it is carried out in Britain. May I therefore explain the procedure in the mass campaign for his information ?

Whereas in Britain vaccination is now given to children when they are 13 years of age, in the mass campaign in India and elsewhere vaccination is given to all children except those under one year of age, the upper age-limit being, in general, the youngest age-group in which 90% are reactors to tuberculin. In practice, this includes adolescents aged up to 20 years. Thus practically all the non-reacting children under 20 years, except those under one, are eligible for vaccination, and not merely 10% as Dr. James seems to think. He has wrongly assumed that the age of vaccination in India in the mass campaign is the same

as that of children vaccinated in Britain, viz., 13 years, and laments the tragic misfortune that in countries like India B.C.G. has been accepted almost as an inexpensive alternative to treatment of infectious cases.

It is indeed a great pity that some medical men in distant lands with no personal knowledge of the utterly different conditions in India should assume the role of advisers. Perhaps it may interest Dr. James to know that in India there are to-day only 23,000 beds for tuberculosis, while the number of infectious cases of tuberculosis is estimated variously at one and a half to two and a half millions. Therefore the main problem was to try and reduce the number of new infections and new cases of tuberculosis, and as quickly as possible, with the available resources. India did well in accepting B.C.G. mass vaccination on the advice of the W.H.O. as early as 1952. The second report of the M.R.C. Committee amply confirms the wisdom of such action, for there is now no doubt that B.C.G. is just as important for the control of tuberculosis in the less fortunate countries as the use of anti-tuberculous drugs, whatever opinion Dr. James and others of his way of thinking may hold.—I am, etc.,

Madras, India. K. S. RANGANATHAN.

REFERENCES

[1] M.R.C. Tuberculosis Vaccines Clinical Trials Committee, *Brit. med. J.*, 1956, **1**, 413.
[2] —— ibid., 1959, **2**, 379.

Ceiling of the Great Hall

SIR,—Perhaps Mr. H. Austen Hall's letter in the *Journal* of February 6 (p. 421) will again focus attention on our Great Hall. I feel that it is no longer deserving of the capital G, as the Association has now outgrown it.

As important as completing the ceiling is the investigation of the possibility of enlarging the seating space. The only suggestion I can recall is to cut the foot to fit the shoe, and prune down the Representative Body. I would welcome the comments of somebody so interested as Mr. Hall.

There appears to me to be a tremendous waste of space at the back beneath the balcony. I believe that reconstruction here would entail the removal of a food lift. Why not? I have only seen it in action once, and that was one morning after arriving on the early train from Scotland, long before coffee was ready in the dining-room. It sailed past me laden with a sumptuous breakfast of bacon and egg for somebody in the upper stories. Would it not be possible to extend the gallery all round the hall to provide at least a few more rows of seats?

We are not the only association finding difficulty in accommodating our conferences, and we might well recoup some of our outlay by letting to other bodies.—I am, etc.,

Stanley, Perthshire. OWEN MCDONAGH.

"Family Doctor" on Food

SIR,—It was a relief to see Dr. Walter W. Yellowlees's letter on this subject (*Journal*, February 6, p. 426). The *Family Doctor* appears to be unaware of the important work carried out by McCarrison and Sanderson Wells, or of the evidence of the "Medical Testament on Nutrition and its Relation to Agriculture" which was published in the *Supplement* (April 15, 1939, p. 157). All is summarized in Doris Grant's book, *Your Daily Bread*,[1] a little volume which I have prescribed for many patients. During the last war I baked all my bread with wholewheat, compost-grown, stone-ground flour. That ensured a delicious and nourishing bread, far removed from the emasculated, blanched, tasteless, white-flour loaves which most bakers produce. When, recently, a lower extraction rate was introduced, the *Lancet*[2] had a leader entitled "The Millers Decide." I trust that this letter will induce many to bake their own bread if they cannot find a baker to supply a vitamin-containing loaf.—I am, etc.,

London, W.1. AGNES SAVILL.

REFERENCES

[1] Grant, D., *Your Daily Bread*, 1944, Faber and Faber, London.
[2] *Lancet*, 1956, **1**, 895.

SIR,—Dr. W. W. Yellowlees, in his letter (*Journal*, February 6, p. 426) seems to imply that honey and semi-refined sugar are much less liable to cause dental caries than sucrose is. There is little evidence for this belief. The valuable factor lost by refinement is the fibre in sugar-cane, fruit, and vegetables. Honey in the comb might be harmless, the wax having a similar cleansing effect to that of the cellular matrix of food plants, but this is doubtful.

I agree that *Family Doctor* ought not in any way to encourage or excuse the consumption of sugar and flour by those with natural teeth. To call these foods valuable is a misleading way of stating the obvious fact that they are cheap, convenient, and pleasant. They could presumably be used as ingredients for wholesome foods incorporating some factors to simulate the chewable texture of fruit, but this has not yet been attempted. At present the only wholesome use for extracted sugar is as a condiment applied to nuts, fruit, and chicle gum, and possibly with fruit juices. *Family Doctor* could help to create a demand for a wider range of wholesome confectionery.—I am, etc.,

London, S.W.10. R. B. D. STOCKER.

Bathing in Sewage-polluted Waters

SIR,—In your leading article on this subject (*Journal*, January 30, p. 336) you rightly state that the figures for Beach "J" are apparently missing from the Table said to record its degree of pollution (Table 3 of the paper in the *Journal of Hygiene*[1]). I hope most readers of the paper will have realized from the context that the code letter "I" ascribed to the second beach listed in Table 3 should have read "J." This error is being corrected in the circulated reprints of the paper. It does not occur in *Medical Research Council Memorandum, No. 37*,[2] as code letters are not used in the paragraph concerned (p. 21).—I am, etc.,

Public Health Laboratory, Exeter. B. MOORE.

REFERENCES

[1] *J. Hyg. (Lond.)*, 1959, **57**, 435.
[2] *Sewage Contamination of Bathing Beaches in England and Wales*, Medical Research Council Memorandum, No. 37, 1959. H.M.S.O., London.

POINTS FROM LETTERS

Anaesthetic Vomiting

Dr. N. K. ALLAHBADIA (Scarsdale Hospital, Chesterfield) writes: I read with interest Dr. F. D. Adrianvala's letter (*Journal*, January 16, p. 203) about anaesthetic vomiting. Obstetric patients have a special tendency to vomit, and inhalation of vomit is recognized as one of the avoidable causes of maternal death. Not infrequently, I have admitted patients from the district with complicated second stage post-partum haemorrhage or incomplete abortion who have had "small meals," tea, coffee, and brandy, etc. . . . I feel that the general practitioners supervising domiciliary midwifery must leave clear instructions as regards feeding during "abnormal" labour or anticipated emergency.

Obituary

GEORGE MacFEAT, O.B.E., M.B., C.M.

Dr. George MacFeat, of Douglas, in the upper ward of Lanarkshire, died there on February 10 in his 87th year. He was a very well-known family doctor and a former member of Council of the British Medical Association, of which he became a Fellow last year. He remained in active practice till a few months before his death.

George MacFeat was born on November 11, 1872, and graduated in medicine from the University of Glasgow at the age of 21. After holding house appointments in the old Glasgow Royal Infirmary, he gained some experience in general practice and then set up for himself in the village of Douglas at the age of 26. There he remained for more than sixty years, serving the farming and mining communities of his area with energy and devotion, as beloved physician and friend.

Early in his career MacFeat took over the Douglas Cottage Hospital from Lady Home, formed a committee of management, and ran it successfully until it was incorporated in the National Health Service.

An indefatigable worker for the B.M.A., he held strong views about the work of the family doctor and his place in the National Health Service. He was chairman of the Lanarkshire Division in 1931–2, served as a representative of his division at many Annual Meetings, and was at one time chairman of the Scottish Committee and president of the Glasgow and West of Scotland Branch. Besides being a member of the Council of the B.M.A., he was for a short time a member of the G.M.S. Committee and of numerous other central committees.

In 1948 he was at once elected to the Lanarkshire local medical committee and in the following year he was made vice-chairman of the Scottish Standing Advisory Committee on General Practitioner Services. He was also appointed one of the original members of the Western Regional Hospital Board, on which he spent anxious days striving to secure that the grading of hospital staff was carried out with the maximum of fairness. The association of the general practitioner with the hospital service was one of the subjects on which he wrote and spoke with authority. In 1950 he was presented with an oil painting in recognition of his services to the medical profession in Scotland.

Dr. MacFeat's wife survives him.

A. S. writes: George MacFeat was a soft-spoken imperturbable man, but he had a dour perseverance and burned with a fierce energy for his patients' well-being, particularly the miners, and it was principally due to his initiative that the Miners' Rehabilitation Centre under the late Sandy Miller was established at Uddingston. For this rehabilitation work he was appointed O.B.E. He always felt that his most fruitful years were during his tenure of the chair of the Scottish Committee from 1946 till 1949, and he was delighted when he was told that his old committee was now the Scottish Council.

He enjoyed a convivial evening with his cronies, such as J. B. Miller, Laird of Cambuslang, and John Reid of Motherwell, all, alas, gone before him. At the annual dinner of the Scottish Midland and Western Medical Association, where at one stage in the proceedings it is customary for each member to arise and state his name and place and date of qualification, he, the most venerable of them all, would promptly proclaim "MacFeat, Glasgow University, 1893," and a great cheer would go up from all the company. The cheer is ringing still, for no practitioner in the Lowlands of Scotland ever embodied the virtues of his race more notably than he did. It is pleasant to remember that the evening of his days was made happy by the honour of the Fellowship of the British Medical Association, which he had so faithfully served.

O. F. H. ATKEY, C.M.G., M.B., F.R.C.S.

Dr. O. F. H. Atkey, formerly director of the Sudan Medical Service, died at his home in London on February 11 He was 81 years of age.

Oliver Francis Haynes Atkey, who came of a legal family, was born on April 11, 1878. From Highgate School he went on to King's College and King's College Hospital, qualifying in 1903 and graduating M.B., B.S. in the following year. After holding house appointments at his teaching hospital, he was for a time resident surgical officer at the Royal Free Hospital and then took the F.R.C.S. in 1905. He joined the Sudan Medical Service in 1907, three years after its inauguration, thus following in the footsteps of his friend, Edward Crispin. Fifteen years later he succeeded Crispin as director of the service, a post which he held for 11 years, from 1922 to 1933. He was appointed C.M.G. in 1929.

H. C. S. writes: it was during the period of Oliver Atkey's directorship of the Sudan Medical Service that the first large expansion of medical work took place. Statistics for hospital admissions, out-patient attendances, and for operations all showed a fourfold increase, and the area of the country brought under effective medical control was nearly doubled. Possibly the most significant advance was in the training of Sudanese medical staff. The Kitchener Medical School, the first in Northern Tropical Africa to provide a comprehensive training for doctors, was opened in 1924. It was due almost entirely to Atkey's personal efforts that the money was raised to pay for the school buildings and to provide the nucleus (of about £E.24,000) for an endowment fund.

It was Atkey's view from the start of the school that it should have some contact with the general world of medicine, and for that reason he established the principle that competent assessors should be present to watch the carrying out of the final examinations and should be given the opportunity of expressing criticism and advice after an inspection of the various departments of the school. Distinguished members of the profession, mainly from the London teaching schools, were invited, and the reports they rendered were of the greatest value. Other training schemes that were either started or greatly developed under Atkey's inspiration were for the midwives, nurses, medical assistants, and public-health officers.

Atkey was an all-out enthusiast. He was a keen horseman and played polo with vigour that was apt at times to be an embarrassment to the opposing side. After his retirement he took up flying, at which his wife was already an adept. Together in the later nineteen-thirties they made many flights over Europe, but an attempt to visit South Africa by air from Cairo ended with a crash landing in Tanganyika and with it Atkey's career as an airman.

He did not continue to practise after leaving the Sudan, but during the second world war he was employed in the inspection of first-aid posts throughout the London regional area. He had been in poor health for the last three or four years and this seriously limited his activities, a privation he bore with exemplary fortitude.

W. F. WILSON, M.B., B.S.

Mr. W. F. Wilson, formerly honorary consulting surgeon to the ear, nose, and throat department of the Royal Victoria Infirmary, Newcastle upon Tyne, and lecturer in his specialty in the University, died at his home at Hove, Sussex, on January 17. He was 79 years of age.

William Frank Willson was born at Newcastle upon Tyne on September 22, 1880, the son of Mr. Adam Wilson, J.P., F.R.C.S., and was educated at Sedbergh and the College of Medicine of the University of Durham, graduating

M.B., B.S. in 1904. After holding the post of house-surgeon at the ("old") Infirmary. He was in general practice for a few years with his father. He later became interested in throat, nose, and ear work and gained a junior appointment in that department of what was by then the new Royal Victoria Infirmary. In 1910 he attended clinics in Vienna, and on his return to Newcastle became assistant surgeon to the late Mr. Samuel Whillis, who was then in charge of the department. This association with Mr. Whillis continued until 1930, when Mr. Wilson succeeded to full charge. He remained in charge of the department until his retirement in 1940. During the first world war he served as a captain in the R.A.M.C.

A frequent attender at the meetings of the Otological and Laryngological Section of the Royal Society of Medicine, Mr. Wilson was also an active supporter of the B.M.A., being secretary of the Section of Oto-rhino-laryngology at the Annual Meeting in Newcastle in 1921 and vice-president of the Section of Otology at the Annual Meeting in Glasgow in the following year. In 1936 he held the presidential chair of the Northern Counties Medical Society. Although a poor "time-keeper" he managed to get through a vast amount of work, both in hospital and in his large private practice.

Keen on outdoor sport, he was regarded as a good shot, a keen angler, and an expert golfer, being a prominent member for many years of the Northumberland Golf Club. Of all his golfing "outings" he probably enjoyed most the spring and autumn meetings with R. J. Willan's Dormie Club at Silloth-on-Solway and the annual "Derby" against the Edinburgh colleges.

Frank, as he was called by most of his colleagues, was a kindly man, loved by his friends and respected by all who knew him. His work and teaching will long be remembered in Newcastle. He leaves a widow, a son, and a daughter, and all in the North extend to them heart-felt sympathy in their great loss.—A. H. W.

E. J. MITCHELL, M.B., Ch.B., D.O.

Dr. E. J. Mitchell, consultant ophthalmic surgeon to the Blackburn group of hospitals, died on January 24, after a prolonged illness. He was 48 years of age.

Edward Joseph Mitchell was born at Northenden, Manchester, on January 8, 1912, and was educated at Xaverian College, Manchester, Cotton College, Staffordshire, and Manchester University, graduating M.B., Ch.B. in 1936. He then held various hospital appointments, including those of senior medical officer and senior registrar and resident surgical officer to the Manchester Royal Eye Hospital. During the second world war he served for four years in the R.A.M.C. as an ophthalmologist, most of the time being spent in the Middle East, where he made many friends and had a very high reputation as an eye surgeon. He took the D.O. of Oxford in 1947, and was appointed consultant ophthalmologist to the Blackburn group of hospitals in 1951.

T. S. writes: The specialty of ophthalmology has suffered a severe blow with the death of Dr. E. J. Mitchell. We, his friends, feel sore at heart when we realize that no more will we enjoy his counsel and companionship. He endeared himself to all who were fortunate enough to know him. His sincerity, his humility, his unselfish eagerness to help his patients, his staff, and his colleagues were the characteristics which made him loved by all. He had a serene, warm, and friendly personality and radiated a sense of ease and contentment. He showed outstanding ability in his work on ophthalmologist and an administrator. His gentleness, his clarity of thought, and the high standard of his work enabled him to gather round him a very devoted and efficient staff who deeply mourn his death. He was rarely known to miss a scientific meeting, as he was ever anxious to keep in the forefront of knowledge.

He was interested in many forms of sport and athletics, his main interest being sailing. He was secretary to the North-east Lancashire Guild of St. Luke, Ss. Cosmas and Damien, to which he introduced many new members; and he was also social secretary to the Blackburn and District Medical Society. He was in large measure responsible for introducing an Order of Sisters who founded the Nursing Home of Our Lady of Compassion in Blackburn, where he died, and it was a great source of comfort to him before his death that this nursing-home was so much appreciated in the district. He has earned for himself a name which will ever live in Blackburn.

To his wife Dorothy, his son Sean, and his daughter Kathleen, we offer our deep sympathy.

T. D. STUART SHAW, M.B., C.M.

Dr. T. D. S. Shaw, who was for many years in practice at Lichfield, died at Castle Douglas, Kirkcudbrightshire, on January 6. He was 89.

Thomas David Stuart Shaw was born on June 23, 1870. He studied medicine at Edinburgh, graduating M.B., C.M. in 1894. After about ten years in practice in Cirencester he moved to Lichfield during the early years of this century, and remained there until after his retirement in 1945. He had been a member of the B.M.A. for 63 years.

G. J. G. D. writes: The death of Dr. T. D. Stuart Shaw after 14 years' retirement recalls him to the memory of those who worked in close contact with him. Although I knew him for the last ten years only of his long professional career, I yet retain many pleasant and stimulating impressions of his sterling character. Of a retiring disposition and never seeking easy popularity, he nevertheless endeared himself to his patients, and their confidence in him was truly inspiring. His devotion to his local hospital was outstanding, and it was, indeed, largely due to his initiative and enthusiasm that the present Victoria Hospital, Lichfield, was built by public subscription in 1933. He also supplied much of the drive that achieved the completion of an added maternity unit a few weeks before the outbreak of the second world war. He served this hospital well as chairman of its executive committee right up to the time of his retirement at the end of 1945. He is survived by his only daughter and three grandchildren. In extending to them our sympathy in their loss, we can also assure them that they have every reason to remember with pride a life very usefully spent.

C. J. A. N. MERCIER, M.B.

Dr. C. J. A. N. Mercier, who was in practice in East Ham for over 45 years, died in New End Hospital, Hampstead, on January 8, at the age of 83.

Charles Jerome Alexander Nicolai Mercier was born on April 9, 1876, and was educated at Antigua Grammar School in the Leeward Islands, where his father was auditor-general. Returning to England in 1896 after his father's death, he studied medicine at Charing Cross Hospital, winning the Llewellyn scholarship and the Golding prize, and graduating M.B. in 1903. After holding an appointment as house-physician at Charing Cross Hospital, he went into general practice at East Ham, first in partnership and later, after the first world war, on his own. During the war he was on active service from 1914 to 1918 in Flanders and in France, where he met his future wife.

As consulting physician and, for a time, senior resident medical officer at St. Mary's Hospital, Plaistow, Dr. Mercier contributed fully to the work of local hospitals. He was a medical officer of the British Red Cross Society, and from 1938 to 1941 a member of the local recruiting medical board. When the second world war began he was in his middle sixties, but as medical officer in charge of the Katherine Road first-aid post he attended to many who

suffered under the severe bombing attacks on London's East End. In 1941 he temporarily left East Ham to act as locum tenens for the holders of two large country practices in Suffolk, so that younger men might remain away on active service. Returning to East Ham in 1945, he continued in practice until 1952, when he retired to Kensington and later to Hampstead.

Dr. Mercier had a keen intellectual curiosity in matters outside his profession. A good conversationalist, he could also listen patiently to the persistent, and a dry sense of humour was never far away. He was especially an enthusiastic, though undogmatic, churchman. During the last four years of his life he faced increasing and painful physical disability with characteristic courage and lack of complaint. Many who were his patients will recall a family doctor who never spared himself, a perfectionist in his standards of service and devotion. He leaves a widow, two sons, and a daughter, to whom we extend our sympathy.

A. macI. macLACHLAINN, M.B., Ch.B.

Dr. A. macI. macLachlainn, of Tobermory, died on October 9, 1959, aged 67.

N. J. N. writes: The death of Alastair macIntosh macLachlainn in the Edinburgh Royal Infirmary on October 9, 1959, came as sad news to his many friends. He was educated at Cargilfield, Cheltenham College, Merton College, Oxford, and Edinburgh University. He read classics at Oxford, but felt an urge to continue his career in his own country and began the study of medicine at Edinburgh in 1912. He was in many ways an idealist and would not appear for a professional examination until he felt himself master of the subject. When the first world war began he was a cadet gunner in the Edinburgh University O.T.C., but enlisted in the Scottish Horse, and served in the ambulance section at Gallipoli under the late Colonel Sir Henry Wade, F.R.C.S.Ed.

One of his great achievements after his return to Edinburgh was the reinvigoration of the Edinburgh University Boat Club, of which he was captain. He was the man mainly responsible for the appearance of an Edinburgh University coxed four in the 1919 Peace Regatta at Henley, and he never lost interest in rowing. A fine long-distance runner, he gave much time and energy to reviving the hare and hounds section of the Edinburgh University Athletic Club. He was the only man running on foot ever to win the "Ramsay Lodge TT"—22 miles from Edinburgh to Peebles. This event was a very carefully handicapped race in which competitors might choose their own method of locomotion—for example, car, motor-cycle, horse, aeroplane, etc.

In 1927 he married Miss Dorothy Vetch, and about this time he discontinued the study of medicine, going to live on his property in Tobermory, Isle of Mull. He was a keen Gaelic scholar and was one of those responsible for reviving the Mull Mod in 1937. He also reorganized the Mull Highland Games.

In 1939 he joined the Argyll and Sutherland Highlanders as a private, but was not allowed overseas, and so in 1941 he returned to Edinburgh and resumed the study of medicine. He graduated M.B., Ch.B. in 1943 and thereafter, as a major in the R.A.M.C., served mainly in troopships in different parts of the world. He held house appointments in the Edinburgh Royal Infirmary and was an assistant physician at the Edinburgh Hospital for Mental and Nervous Diseases. For a short time he served as medical officer on board a whaler off South Georgia.

When we look back on our lives and on our student days there are men of whom we never think again. There are others to whom our minds are constantly returning. macLachlainn was one of the latter. It would be fair to describe him as an original and brilliant eccentric. He had a high degree of literary ability, a great intellect, and a keen sense of humour. He was a patriot and a generous and staunch friend. He leaves a widow, two daughters, and a son.

R. H. PEARCE, M.R.C.S., L.R.C.P.

Dr. R. H. Pearce, medical officer of St. Leonard's Hospital, Ringwood, Hants, and formerly in practice in Birmingham, died at the Central Middlesex Hospital on January 20. He was 66 years of age.

Reginald Hickmott Pearce was born at Cardiff on September 3, 1893, and educated at Rishworth School, Yorkshire. After obtaining a pharmaceutical qualification, he volunteered for service in the first world war. On demobilization he studied medicine at Birmingham University, qualifying in 1926. He then went into practice in the Northfield area of Birmingham, where he remained for the next 20 years. Moving to Ferndown in Dorset, a place which he loved, he served on the Ministry of Pensions boards there, and for eight years he was medical officer of St. Leonard's Hospital, Ringwood, where he was much loved.

Dr. Pearce married Eleanor Mary, daughter of J. W. Russell, of Balliol College, Oxford. Our sympathy is extended to her and their daughter.

WILLIAM HOEY, M.B., B.Ch., B.A.O.

Dr. William Hoey, who practised in Wigan, died in that town on January 25. He was 65 years of age.

William Hoey was an Ulsterman. Born on May 20, 1895, he was educated at the Royal Belfast Academical Institution and Queen's University, Belfast. His medical studies at Queen's University were interrupted by the first world war, in which he served in the Machine Gun Corps in Gallipoli and France. After the war he returned to Queen's University, graduating M.B., B.Ch., B.A.O. in 1921. During his academic career he gained several distinctions and was also prominent in athletics. After qualification he entered general practice, working in Lancashire and Staffordshire before going to Wigan in 1926, where he remained for the rest of his life.

Dr. Hoey took a keen interest in surgery and was on the staff of the Royal Alfred Edward Infirmary until the start of the National Health Service, after which he became honorary consulting surgeon. He was police surgeon to the borough and also took an active part in the affairs of Wigan Rugby League Football Club as its honorary surgeon for many years. When he retired from this post in 1958 the club elected him to life membership, an honour he greatly valued. He served upon many statutory medical boards and panels, but his main interest was in the people who formed his practice, for whom his feelings always extended beyond the purely professional. A long-standing member of the B.M.A., he was chairman of the Wigan Division from 1950 to 1951. His later years were marred by serious ill-health, but his concern for his patients did not decrease, and his death at a comparatively early age is mourned not only by colleagues but by a large number of those in whose service his life was spent.

J. P. J. writes: Dr. William Hoey, or Bill as he was affectionately known, came to Wigan in 1926 after a short period in the Midlands, and became associated with Dr. Elisha Monks, one of the great G.P.s of the later Victorian era, and therefore a difficult man to follow. However, this was no trouble to Bill, and certainly the practice did not suffer when he had to take over. Of quiet disposition and speech, he preferred to listen rather than to talk. His judgment was sound, and he was a good comrade to have at one's side in an emergency and his help was always freely given. His wants were simple, and he enjoyed his golf and quiet leisure in his home and garden. We in Wigan mourn his passing after a long and distressing chest complaint and will miss this sterling man from Ulster, a country which seems to produce men of character and determination. His wife, being of the same calibre, will surely be a great comfort to their four daughters in their bereavement.

LILIAN LINDSAY, C.B.E., LL.D., F.D.S. R.C.S.

Dr. Lilian Lindsay died on January 31 at the age of 89. She was the first woman in Britain to become a dental surgeon, and she achieved fame and honour in her profession.

Lilian Lindsay went to Edinburgh to study dentistry, since women were not admitted to the qualifying examination in England. She took the diploma of L.D.S. R.C.S.Ed. in 1895. Later she practised with her husband, Mr. Robert Lindsay, in Edinburgh, but moved to London when her husband became the first whole-time dental secretary of the British Dental Association. The work of the Lindsays for the British Dental Association was outstanding, and the library which Lilian Lindsay first began to build up is now one of the best in the world, and is known as the Robert and Lilian Lindsay Library. Lilian Lindsay was president of the B.D.A. in 1946 and was elected F.D.S. R.C.S. in the following year. She was an authoritative historian of dentistry, was the author of a short work on the subject, and had the unusual distinction of being president of the section of the history of medicine of the Royal Society of Medicine from 1950 to 1952. It was when the British Dental Association was meeting in Edinburgh in 1946 that the honorary degree of LL.D. was conferred upon her. In the same year she was appointed C.B.E.

E. P. CAREY, M.B., B.Ch., B.Sc., LL.D.(Hon.)

The obituary of Dr. E. P. Carey was published in the *Journal* of January 16 (p. 207).

D. J. C. writes from Co. Dublin: I am proud to say that I was one of Ned Carey's most intimate friends. During our student days we saw a great deal of each other, meeting in good times and in bad, and when our fortunes were at their darkest Carey's irrepressible humour never failed to dispel the gloom. His brand of humour might occasionally have been sardonic, but never malicious. Like many humorists, he was deeply religious, and his faith was in fact the key to our understanding of his admirable qualities. Those of us who came under the spell of his magnetic personality will easily understand his gift for making friends. Thanks to his natural gaiety, lack of pretentiousness, and compelling personality, he was enabled to give life and continuity to the many London-Irish organizations over which he presided.

During the first world war he served as a doctor in France and Gallipoli. After he had been demobilized he served in the Irish war of independence. Despite his change of allegiance, I was informed that he had as much love and regard for his English acquaintances as he had for his fellow countrymen. "Love your neighbour, no matter who or what he is, or to what school of political or theological thought he belongs": that was Carey's motto —the motto of a Christian humanist. His death will leave a wide gap in the lives of all who knew and loved him.

MAX THOREK, M.D.

The obituary of Professor Max Thorek was published in the *B.M.J.* of February 6 (p. 431).

Mr. PAUL QUINET writes from Solihull: Up to ten years ago Max Thorek was only a name to me, a name attached to many operative techniques, the best-known one being the Max Thorek operation for undescended testicles. Then I was fortunate enough to make his acquaintance, and I have seen him every year since, when he has been presiding at the various conferences of the International College of Surgeons in most of the European capitals, and I became very attached to him. Max Thorek was a great man who thought that it was nice to be important but much more important to be nice. He always welcomed everyone in a charming way, and went to enormous trouble to help other people. He was loved and admired by all who came in contact with him. At his conferences he was a polished orator; he always had some interesting and new ideas to put forward

His thoughts in life followed those of Pasteur, who said, "La Science n'a pas de patrie," and his aim in life was for the advancement of surgery and the relief of suffering for mankind. The amount of work he did during the last ten years was enormous. He presided constantly over conferences in every continent, and never spared himself, in spite of the fact that a few years ago, whilst in Geneva, he was taken very ill. However, he made little of it, and after recovering he worked as hard as before.

Max's knowledge of surgery was prodigious, and he was constantly reading new articles published in various parts of the world. Being a very good linguist, he was able to read these in the original form.

Max Thorek was not only a great surgeon but he was a philosopher and a great pioneer of a new idea for surgeons—the idea of having a huge family of all the surgeons of the world. I believe he had been thinking of this idea since he became a young surgeon, and it finally came to fruition in Geneva 25 years ago, when he founded the International College of Surgeons, which has 14,000 members to-day. He acquired an enormous number of very influential friends in every country he visited. The college he established with such firm foundations will live for ever, and his good work will continue to flourish with the help of his son and his officers, who are heart and soul in the work he started. I know that every one of the surgeons who has known Max will mourn his loss and will treasure the memories they have of him. His name in surgery will live for ever as one of the outstanding surgeons of all time. My sympathy goes out to his wife and son.

R. E. APPERLY, M.R.C.S., L.R.C.P., F.F.A. R.C.S.

The obituary of Dr. R. E. Apperly was published in the *Journal* of February 6 (p. 430).

Dr. M. H. W. HOLLOWAY writes: No doubt others more qualified to do so than myself will record their appreciation of the long and distinguished services to anaesthesia and to the Middlesex Hospital in particular rendered by the late Dr. Raymond Apperly. I should, however, like to contribute a few personal reminiscences. Raymond Apperly was born and bred in the Cotswolds, and it was to the Cotswolds that he retired in 1944, settling at Painswick and then at Minchinhampton and finally spending the last two or three years of his life in Evesham, in order to be near his son who was in general practice there.

He was the son of Ebenezer Apperly, a busy dentist in Stroud, and the grandson of Sir Alfred Apperly, the founder of the Apperly and Curtis cloth mills. From his father he acquired an interest in anaesthetics at an early age; this was no doubt due to his father having installed a small apparatus in a shed in the garden for the manufacture of nitrous oxide, whence it was piped into the surgery—surely one of the earliest examples of an anaesthetic pipe-line in the country. Though his career ended before the acceptance of some of the present-day methods and techniques of anaesthesia, he nevertheless maintained a keen and lively interest in all matters connected with his specialty in his retirement.

In the course of many years practising anaesthetics a large number of incidents occurred which tickled his well-marked sense of humour. Characteristically, the only stories with a sting in the tail were directed against himself. It amused him to think that he must have been one of the very few anaesthetists (if not the only one) to have operated on a president of the Royal College of Surgeons—having removed under local analgesia a small sebaceous cyst from Sir John Bland-Sutton's arm. He was justifiably proud of having been the first man to demonstrate spinal analgesia to the surgeons and anaesthetists at St. Thomas's Hospital in 1908 and also of having been asked to be the first

examiner for the D.A. when it was introduced, an appointment he declined for personal reasons.

His passing is a very real loss, and every sympathy is extended to his widow, son, and daughter.

WU LIEN-TEH, M.D., Sc.D., Litt.D., LL.D., M.P.H.

The obituary of Dr. Wu Lien-Teh was published in the *Journal* of February 6 (p. 429).

Professor W. C. W. NIXON writes: Wu Lien-Teh was a remarkable man, for he was able to enjoy the best of both worlds—the East with its wisdom and the West with its scientific practice. He held fast to the traditions and philosophy of his forebears despite the many years he spent in Europe and the United States.

I have reason to be grateful to him for his advice and kindness when I found myself, an occidental, in the Orient. We had a common interest in that we graduated from St. Mary's Hospital, and on the occasions he visited Hong Kong he would reminisce on his happy student days at Cambridge and in London. He was ever grateful for the friendship of Sir Zachary Cope and Professor T. R. Elliott, first full-time professor of medicine at University College Hospital.

Most of us start contemplating retirement after the age of 60, but not Wu Lien-Teh. I travelled with him and his family in 1937 from Hong Kong to Singapore after the Japanese had overrun Shanghai. His beautiful home and valuable collection of ancient Chinese medical books had been burnt. I recall his fervour when he said, "I am 60 and have lost everything, but I shall not give up medicine. I shall open a dispensary in Malaya." Ironically he was to suffer from the Japanese again a few years later when they occupied Malaya. Undaunted, he started to practise again after their defeat.

He, more than any other Chinese, laid the foundations of a modern medical service for his country. It is fortunate that posterity will have in his autobiography—*Plague Fighter*—a record of the achievements of this great doctor.

H. H. RAYNER, M.B., Ch.B., F.R.C.S.

The obituary of Mr. H. H. Rayner was published in the *B.M.J.* of February 6 (p. 430).

Mr. THOMAS MOORE writes: As Mr. H. H. Rayner's chief assistant at the Manchester Royal Infirmary I soon realized how fortunate I had been to be associated with one so skilled in his profession. It was evident that he was regarded by all his colleagues, particularly his most critical juniors, as the soundest opinion and the safest hands in the district. In an age when surgical techniques were developing very rapidly and to operate was to become easier than to diagnose, he acted in the Manchester school as a break on the worship of mere surgical technique and a signpost to the more difficult but safer road of accurate pre-operative diagnosis, followed, where necessary, by definitive and not exploratory surgery. Frequently he used to say, "There is always time to make a diagnosis." Possessed of a fine clinical acumen he despised the laparotomists.

In the theatre he was careful, gentle, and deliberate. All flashy and slick operating was anathema to him. None of his assistants was allowed to tie ligatures one-handed. "In surgery life literally hangs by a thread, and it is important to see that it is tied securely." Nothing was ever left to chance: he is known to have taken down the whole of a gastroenterostomy and do it again as he was not quite satisfied by the first effort. The care and gentleness he practised in the theatre were reflected by the excellence of his post-operative results. It was generally recognized that his patients were never "shocked," no matter how long or difficult the operation.

"Bertie" Rayner, as he was affectionately known by colleagues and students alike, was a definite character in the Manchester medical school. He was no slave to surgery and did not carry out long operating lists. Taking care of his own health and comfort was to him an important factor in giving the best service to his patients. Thus, he was no enthusiast for surgery during the night, believing that all medical and nursing personnel work much better during the following day after a good night's rest. In his view it was rarely necessary to operate as an emergency, and he had not to be disturbed once he left the hospital. In private practice, too, the same principles applied.

Blessed with a high degree of intelligence he understood many surgical problems much before his time. He was practising the conservative treatment of the late case of appendicitis before it was published and popularized by Ochsner and Sherren. In gastro-intestinal surgery, to make the patient safe for surgery was his routine long before it became orthodox practice. During my long association with him one could not but be impressed by his absolute professional, intellectual, and moral honesty. All difficulties were thrashed out quite openly, and he could never be a party to deceit. This characteristic possibly made him not a very good committee-man, and he took little or no interest in medical or hospital administration.

In 1945, on retiring completely from the active staff of the Manchester Royal Infirmary, he continued to serve for some years as consultant surgeon at Altrincham General Hospital, where he did much to bring the hospital up to a high standard of efficiency. On his retirement from this hospital his medical colleagues there formed a Rayner Club, which met every year to dine with him. He spent his years of retirement in extensive reading, walking, and learning to service his own car, in which he became very expert.

All his many friends who mourn his passing rejoice for his long and useful life devoid of any serious ill-health or suffering. The Manchester medical school is a better place for having been the alma mater of Bertie Rayner.

A. R. K. writes: I had the honour of being Mr. Rayner's resident surgical officer at Altrincham General Hospital. He was so diffident that it was only afterwards that one realized how much one had learned while working with him. His only concern was the right treatment for the particular patient. He used to say that the proper practice of surgery consisted of three stages—(1) diagnosis; (2) diagnosis; and (3) diagnosis. When told that a cholecystogram had been arranged for a patient, he said, "Whatever for? Isn't it quite obvious that she has cholecystitis?" He remembered every stitch he put in in an operation, so that no complication seemed to surprise him. He had already considered the risks and possibilities. It might be teasingly related that at any cocktail party "Bertie" could be heard quietly discussing the symptoms of chronic appendicitis; but (and here was the acid test) ask any doctor in the Manchester area whom he would have for his surgeon, and the answer never varied. Safety and humanity are the things that matter when you're the patient.

Sir ROBERT HUTCHISON, Bt., M.D., LL.D., D.Sc. F.R.C.P., Hon.F.R.C.P.Ed.

The obituary of Sir Robert Hutchison was published in the *B.M.J.* of February 20 (p. 571).

Dr. J. R. B. DIXEY writes: It is as though an era has passed, now that Sir Robert Hutchison has died. There will be many to tell of his astonishing achievements who knew him because they worked under him and for him. This is by way of a postscript from one who knew him in his latter days and who gained his friendship at the end of his long life. I had the honour, the privilege, and the enormous pleasure to be his doctor during his last few years. He was the easiest of patients because he always accepted the advice given without demur—"There is no use in sending for a doctor if you don't do what he tells you"—but seldom without some comment on advances in medical science.

"When Modern Medicine (M.M.) has exhausted the patient, Modern Therapy (M.T.) is there to finish him off, and if that fails there is always a physiotherapist lurking in the background to do the job." How he scorned the practice of referring to everything by its initials. He once told me that he knew what A.C.T.H. stood for: has "A Cruel Therapeutic Hoax" ever yet been bettered as a definition? How he loved to make good-humoured fun of anything that smacked of jargon, and to pretend to believe that modern practice owes nothing to the art of medicine as he knew it!

I make no apology for quoting light-hearted references in this tribute to him, because he certainly would not wish to be remembered in a solemn way. His never-failing wit and wisdom made each visit to him a joy. Having given freely (and always, in the event, with complete accuracy) of his enormous knowledge and experience when asked about any and every clinical problem, he would enlarge about the natural history of such conditions in his day. How many people can remember that, long before Ramstedt's operation, haematemesis in the apparently terminal stages of infantile pyloric stenosis often marked the turning-point which led to eventual recovery? How many can remember asking "the honorary visiting pathologist to be so good as to come to the ward with a view to enumerating the red blood corpuscles"? Of these and many other fascinating things he spoke, and what a treat it was to listen.

His humour was unfailing, his patience unending—"Boredom is the sign of a small mind"—and I feel sure he is where he deserves to be, and where he has long wanted to be. "The trouble with you young doctors is you have not the gumption to finish me off with a decent dose." Of course I had not. Little did he know how I treasured his friendship, and how much it meant to me to be able to attend him, and at the same time to be the last of a very, very long line to sit at his feet.

Medico-Legal

"TRUTH DRUGS"

[FROM OUR LEGAL CORRESPONDENT]

On January 20 Ernest William Kenneth Spencer, of "The Wheatsheaf," Nottingham, a publican aged 42, was found guilty by the jury at Nottingham Quarter Sessions of stealing £420 which had belonged to a dead man (*The Times*, January 21). His neighbour had found her lodger dead and called in Spencer to help. He took the money from the neighbour's house and later panicked and threw it away. It was found in the cellar of "The Wheatsheaf."

Psychiatrist's Evidence

Dr. G. M. Woddis, superintendent of the Coppice Mental Hospital, Mapperley, who was called to give evidence, and who was consulted by Spencer on his solicitor's advice, said that Spencer told him he could not remember taking the money. He treated him at his request with injections of thiopentone and methylamphetamine, which acted as a "truth drug." From his behaviour while under the influence of the drugs Dr. Woddis formed the opinion that Spencer took the money while suffering temporarily from a state of "dissociation" brought on by the shock of seeing the corpse on his neighbour's kitchen floor. Spencer re-enacted what had happened, and Dr. Woddis thought that at some point while helping with the body he mistook it for that of his own father, who had died seven years before. When Spencer described helping his neighbour to open the safe he did so in such a way as to show that he thought he was protecting his late father by taking possession of the money himself.

In his summing up the Recorder, after expressing doubt as to the admissibility of Dr. Woddis's evidence, directed the jury that, since it had been admitted, they should not discredit it simply because such evidence was novel and had in his experience not played an important part in a criminal court in England before. The jury nevertheless found Spencer guilty of theft.

Restrictions on Use

Two years ago we reported a somewhat similar case before the Worthing magistrates (*Journal*, March 15, 1958, p. 651). Here an anaesthetic drug had been used by a psychiatrist, called by the Defence, in forming his diagnosis of the accused's state of mind at the time he took the property he was accused of having stolen. We pointed out that to use a drug of this nature to help elicit the facts necessary for diagnosis would constitute in law an assault unless it was done with the patient's consent, and that, as a matter of professional ethics, without his patient's consent a doctor would not be justified in voluntarily giving evidence of what he had discovered by using such a drug.

In Spencer's case the "truth drug" treatment was administered at his own request and Dr. Woddis was called in his defence, so both these conditions were observed. It is because of these conditions that such evidence is never likely to be available for the prosecution. If it were adduced for the prosecution a jury would not be likely to give it very much weight. In Spencer's case they rejected it even when adduced for the defence.

DRINK, EPILEPSY, MURDER, AND AMNESIA

[FROM OUR LEGAL CORRESPONDENT]

Both Coke and Hale referred to voluntary drunkenness as *dementia affectata*, or acquired madness, and regarded it as an aggravation of the guilt of any crimes committed under its influence. That is not the legal view now. Under the modern criminal law it cannot be pleaded as a matter of excuse that alcohol inflamed the passions of the accused or reduced his self-control, but whether such a plea is a ground for diminishing or increasing sentence depends on the circumstances of each case. Voluntary drunkenness is a defence to a criminal prosecution in two types of case only: (1) Where insanity as defined by the McNaughton Rules supervenes; or (2) where a specific intent is an element of the offence, and the drunkenness was such as to prevent the formation of this intent. Examples of "specific intent" are, on a charge of burglary, the intent to commit a felony in the house broken into, and, on a charge of murder, "malice aforethought," the absence of which will on appropriate facts reduce the crime to manslaughter.

In two recent cases persons charged with murder were found guilty but insane, their insanity being precipitated by drinking.

Epilepsy Provoked by Alcohol Intake

On December 3 at the Central Criminal Court Dennis Coster, a lorry driver aged 41, of Limehouse, was found guilty of murder but insane. He was ordered to be detained as a Broadmoor patient until Her Majesty's pleasure be known (*The Times*, December 3 and 4). Mr. Coster was said to be a man of sober habits living happily with his wife and two sons. On the evening of October 1 Mr. and Mrs. Coster were entertained at the flat of a neighbour, where 24 half-pint (0.3-litre) bottles of lager were consumed, most of them by Mr. Coster and the neighbour. At about midnight Mr. and Mrs. Coster returned to their own flat: Mrs. Coster was sober, but Mr. Coster was drunk though able to stand. During the night voices and then a woman's screams were heard from the flat. The next morning Mr. Coster awoke to find his clothes blood-stained and his wife dead on the floor, her body being covered with bruises. He called the police, and said, "Whatever happened I must have done it, but I do not remember what happened." The prosecution accepted that Mr. Coster's amnesia was genuine.

Evidence was given by Dr. J. C. Sawle Thomas for the defence that Mr. Coster was an incipient epileptic. He stated that the consumption of a large quantity of any fluid, including water, might aggravate an epileptic tendency, but that if the fluid contained alcohol the effect would be much worse. In his opinion Mr. Coster, at the relevant time, was insane within the meaning of the McNaughton Rules. The prosecution did not challenge this evidence, and the jury found their verdict in accordance with it.

Genuine Amnesia

In another recent case of a similar type there was a conflict of evidence concerning the state of mind of the accused at the time of the crime. On October 27 William Alexander Wilkin, a plater's helper aged 32, of Darlington, was found guilty at Durham Assizes of murdering a woman and her 2-year-old son with a hammer, but the jury found he was insane at the time (*Daily Telegraph*, October 28). Wilkin had been drinking before committing the crime. He stated that he could not remember what happened in the dead woman's home.

Dr. J. R. Hawkings, a psychiatrist called for the defence, said that he believed Wilkin to have been suffering from a hypobulic crisis at the time he killed the woman and child, and that he did not realize what he was doing. However, in the opinion of Dr. I. G. W. Pickering, senior medical officer at Durham Prison, called for the prosecution, Wilkin had a hysterical crisis from acute alcoholism after taking "dutch courage" before going to the house where he did the killings, and he knew what he was doing. Dr. Pickering gave it as his opinion that Wilkin's loss of memory was a genuine dissociated amnesia. On the other hand, Dr. J. P. Child, a psychiatrist, also called for the prosecution, attributed Wilkin's amnesia solely to alcohol: he said that, as soon as he started questioning Wilkin about the events, the accused seemed to sober up. Cross-examined, Dr. Child said that Wilkin had not suffered from a disease of the mind, though he was alcoholically insane at the time of the killing.

Wilkin was ordered to be detained during Her Majesty's pleasure.

MEDICAL TREATMENT IN PRISON

[FROM OUR LEGAL CORRESPONDENT]

On January 14 the Court of Criminal Appeal gave Raymond John Cleverley leave to appeal against a sentence of three years' imprisonment, and on February 1 the Court substituted an order of three years' probation with a condition that he should reside at a mental hospital (*The Times*, February 2).

Cleverley, a civil engineer, was convicted on July 23, 1959, of wounding his former fiancée with intent to cause grievous bodily harm. His counsel stated that he suffered from a schizoid personality and pathological shyness. Shortly after his fiancée indicated that she had finished with him, Cleverley bought a knife and some pills containing strychnine, intending to kill his fiancée and himself. In fact he inflicted no more than a superficial flesh wound, as he held back at the crucial moment. Cleverley was granted bail before his trial, and became a voluntary in-patient in a mental hospital. On the advice of the doctor in charge of him, Dr. Alan Capstick, he was discharged from hospital after five weeks to become an out-patient. His condition was markedly improved before his trial, but after his trial and sentence to prison he deteriorated sharply. The following day he made an abortive attempt at suicide.

Association with Homosexuals

Since sentence, Cleverley had been in two prisons. He was first sent to Winchester, where he received no psychiatric treatment; and then, after five months there, on January 13 he was transferred to Wormwood Scrubs, where he was treated in a ward with ten other prisoners, all psychiatric cases, four of whom were homosexuals.

At the appeal Dr. Capstick was called to give fresh evidence of the effect of prison upon Cleverley. Dr. Capstick said that on examining Cleverley before his trial he thought he would be responsive to psychiatric treatment, though this would have to be long-term or perhaps permanent. Under treatment the chances of a recurrence of violence were so slight as to be disregarded. Dr. Capstick examined Cleverley the day before his appeal, and found him changed for the worse: he was more tense, shy, and despondent. The continued talk of homosexuality in the ward at Wormwood Scrubs was causing him to suffer intensely, and if he were kept in prison for a further eighteen months his fitness to be at large could not be guaranteed. A prison medical officer from Wormwood Scrubs was called by the Crown to justify the group therapy to which Cleverley had been submitted.

Court's Powers to Order Treatment

The judgment of the court was delivered by the Lord Chief Justice, who said that, by reason of the fresh medical evidence which had been called, the court would substitute an order for probation for three years with a condition that the appellant should reside at a mental hospital. The court was empowered to make this condition effective for only twelve months, and the twelve months had to run from the date of conviction (i.e., from July 23, 1959). No other order could be made for treatment, and the court looked to the appellant's parents to make arrangements for the future.

The power of the courts to make orders for treatment is severely limited. A court can only make a mandatory order for confinement in a mental institution where the convicted person is found to be insane by the test of the McNaughton Rules. The court has no power, on sentencing a man to prison, to order that he should receive treatment while in prison. The classification and treatment of prisoners is entirely in the hands of the Prison Commissioners, and the prison medical officer is under a duty[1] to report to them, through the governor, if he thinks that a prisoner's mental or physical health is likely to be injuriously affected by continued imprisonment or by any conditions of imprisonment. The court can, however, make a probation order with a condition that the convicted person submits to specified medical treatment for a period of not more than a year. But before any probation order is made the convicted person must consent to its terms. A similar effect can be achieved by a conditional discharge, but by no other means.

Prison Rules

Counsel for the appellant in the present case laid some stress on the fact that for his first five months in prison, while awaiting appeal, Cleverley received no psychiatric treatment. The medical officer of every prison is under a duty[1] to care for the mental and physical health of all the prisoners, including those awaiting trial and those who have lodged appeals. He must visit daily every sick prisoner, every prisoner who complains of illness, and any other prisoner to whom his attention is specially directed, and he may at his discretion call into consultation another medical practitioner. A person awaiting trial (who is presumed innocent) may, with the consent of the Prison Commissioners, call in his own doctor to attend him. A convict who is awaiting the hearing of an appeal has not this privilege, except that his doctor may attend to examine him for the purpose of the appeal.

Fresh evidence, including fresh medical evidence, may be called on an appeal at the discretion of the Court of Criminal Appeal. This evidence may refer to the circumstances of the criminal or to the gravity and effect of the sentence on the individual prisoner. The court must see that the punishment fits both the crime and the criminal. The function of the criminal courts is, however, basically to punish and not to prescribe treatment.

[1] *Prison Rules, 1949*, S.I. 1949, No. 1073.

Medical Notes in Parliament

DRUGS FOR PRIVATE PATIENTS

"The Government have no present plans for legislation" on the subject of drugs for private patients. This was the new fact which appeared when the topic was raised in the House of Lords on February 18 by Lord AIREDALE. His question asked why compulsory contributors to the Health Service, who saved public expense by paying for private consultations, were debarred from receiving medicines and drugs on Health Service terms.

Viscount HAILSHAM, Lord Privy Seal, stated that under section 38 of the Health Service Act provision was made for the supply of medicines only to persons receiving general medical services under the Act. New legislation would therefore be required to enable private patients to be supplied on the same terms. He repeated the Minister of Health's statement that the Government attached importance to the preservation of private practice, and the right of persons to resort thereto and would certainly consider making medicines available to private patients on Health Service terms, in the context of available resources and competing claims, if it were shown that the present position was endangering the existence of private practice or preventing any substantial number from availing themselves of it who would otherwise wish to do so. But the Government had no present plans for legislation on this subject. He added that, as Exchequer expenditure on the remuneration of general practitioners was based not on the number of patients but on the number of practitioners in the Service, there was no automatic saving if patients obtained their medical treatment privately.

RADAR STATION

In a statement in the House of Commons on February 17 the Secretary of State for Air, Mr. GEORGE WARD, admitted that there would be a thermal radiation hazard at a proposed new radar station on Fylingdales Moor, Yorkshire. He said that the Government had agreed with the United States Government to set up and operate "a ballistic missile early warning station" in the United Kingdom, in support of the North Atlantic Treaty. The Fylingdales site comprised about four square miles of land in a National Park. In reply to a question by Mr. G. DE FREITAS (Lincoln, Lab.) about possible radiation dangers, Mr. WARD said: "There will be some thermal radiation. There is no question of any nuclear radiation. There will be a safety area immediately in front of the radar heads. This accounts in large measure for the four square miles we need for the station."

QUESTIONS IN THE COMMONS

Merit Awards for G.P.s

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health on February 22 whether he was aware of the strong feelings among general practitioners against any sort of differential payments scheme; and whether he would take full account of these in considering the recommendation of the Royal Commission on Doctors' Remuneration in this connexion. Mr. D. WALKER-SMITH: Until the Secretary of State for Scotland and I have fully studied the report and its implications it would be premature for me to comment on its recommendations.

Dr. JOHNSON asked if the Minister was aware of the grave fears that any remuneration in the form of merit awards for general practitioners would undermine the medical profession and destroy the doctor–patient relationship. Would he take serious account of such fears that had been expressed in many forms? Mr. WALKER-SMITH said it would be their duty to take into account all relevant considerations when considering the recommendations of this report. Dr. EDITH SUMMERSKILL (Warrington, Lab.) asked the Minister to bear very carefully in mind the point raised, and when the time came would he tell the House exactly what the criteria were that he intended to apply to the general practitioners whom he believed would merit this award. Mr. WALKER-SMITH undertook to bear it in mind, in common with all other relevant considerations. When they had had time to consider the report they proposed to discuss it with the medical and dental professions, and in those discussions no doubt this and other points would come up.

Finding a Locum Tenens

Mr. L. PAVITT (Willesden, West, Lab.) asked if the Minister was aware of the inadequacy of the present arrangements for employing locums in general practice and the hospital services; and what steps he would take to improve the position. Mr. WALKER-SMITH: I am aware that individual difficulties sometimes occur, but I am not clear that action by me would be appropriate. Mr. PAVITT suggested that the Minister might consider the introduction of a scheme for a local service, and the possibility of using the trainee assistants' scheme to help. For example, if a trainee were to give two months at the end of his normal training period to gain wider experience, and also in hospitals, that would help. Would the Minister also consider the possibility of refresher courses for consultants and specialists, so that they might come down into the arena of family doctoring, which might be beneficial to them and help the general practitioner in solving his problem of locums?

Mr. WALKER-SMITH said he doubted whether an organized service of the sort suggested would meet the case, because there were so many and varied personal factors involved. He would like to consider the second suggestion. The third point was revolutionary, and like Agag of old he had better tread delicately. Dr. EDITH SUMMERSKILL asked him to reconsider his answer, pointing out that most doctors were employed by the State, and in the event of illness they found great difficulty in obtaining a deputy. The same applied to their holidays. The Minister might consider the whole field. Mr. WALKER-SMITH said he was ready to consider it further, but the difficulties about locums should not be exaggerated. There had been a considerable increase in the number of general practitioners and hospital doctors, and the difficulties had to be seen against this more satisfactory background.

Assistants Without "A View"

Mr. PAVITT also asked if the Minister would establish uniform criteria to be applied by all local executive councils when reviewing the appointment of assistants in general practice. Mr. WALKER-SMITH replied that the circumstances in which an assistant might be employed varied widely and he did not think it would be desirable to limit executive councils' discretion in the way suggested. Mr. PAVITT said that if there were the same standards it would get rid of the anomaly whereby a person living on one side of a county boundary had different conditions from a person living on the other side. A few general practitioners continued to employ assistants "with a view," and the "view" remained permanently on the horizon. Mr. WALKER-SMITH replied that these difficulties were sought to be met, first, by the requirement of obtaining the consent of the executive council where a doctor wanted to employ an assistant for more than three months; and, secondly, the periodical review of the consents given, introduced in 1956. It was clear that the consents were not necessarily permanent; they were subject to review.

Control of Drugs

Mr. GEORGE DARLING (Sheffield, Hillsborough, Lab.) asked the Minister if he was satisfied with the procedure for testing drugs and for banning the sale, except on medical advice and prescription, of drugs which might otherwise be harmful. Mr. WALKER-SMITH said that he was considering a recommendation by the Committee on the Cost of Prescribing to the effect that the arrangements for testing drugs should be improved. Restriction to supply on medical advice and prescription was a different matter, in respect of which the Home Secretary and he already had powers. An inter-departmental working party was studying the present law, and would make recommendations on any changes which it thought necessary.

Mr. DARLING suggested it was time the confusion between the two departments was ended, and the whole authority placed in the Ministry of Health. No new drugs should be placed on the market until they had been approved by some authority. Mr. WALKER-SMITH denied that there was any confusion. It was true that on the control of drugs there were two departments—the Ministry of Health in regard to therapeutic substances, and the Home Office in regard to the Poisons Act and the Dangerous Drugs Act—but they worked harmoniously together. Dr. EDITH SUMMERSKILL said the Minister should inform the drug houses, who were hawking their high-priced drugs from doctor to doctor, that all drugs should at least have a clinical trial. Mr. WALKER-SMITH told her that consultations with the professional and other bodies on the Hinchliffe recommendation for a clinical trials committee were well advanced, and he hoped to be able to make a statement on that aspect shortly.

New M.R.C. Studies on Radiation

Mr. M. MCLAREN (Bristol, North-west, Con.) on February 18 asked the Minister of Health, as representing the Minister for Science, when the Medical Research Council would report again on the hazards to man of nuclear and allied radiations. Mr. WALKER-SMITH stated that since the publication of their report (Cmd. 9780) in 1956 and their statement on the report of the United Nations Scientific Committee in 1958 (Cmd. 508), the Medical Research Council had kept the subject under constant review and had recently begun to prepare a further report which would provide a comprehensive assessment of the significance of all the available evidence. Much further evidence had been obtained on the levels of radioactivity from various sources and their biological effects, but certain essential data on exposure levels in this country—for example, that from diagnostic radiology—were still incomplete. The Council's report was therefore unlikely to be ready before the summer.

Board of Control Report on Broadmoor Escapes

Mr. W. VAN STRAUBENZEE (Wokingham, Con.) asked the Minister on February 15 whether he had yet received the report of the inquiry by the Board of Control into the escape of Leslie Parr from Broadmoor Institution on January 1; and whether he would make the report public. Mr. D. WALKER-SMITH: The report, which I do not consider it would be appropriate to publish, deals particularly with the circumstances under which patients should be allowed to work outside the walls of the institution. Work of this type is an important last step in the rehabilitation of patients for return to the community, but it is of course essential that there should be proper security arrangements. With this in mind, the report recommends (1) that no patient should be allowed in future to work inside a private house out of the direct observation of the nurse in charge of him; (2) that the work done by all outside working parties must be of such character or so arranged as to allow the closest possible supervision of every patient by the nurse in charge; (3) that specific written instructions to the above effect be issued to nurses in charge of working parties. Arrangements have been made to put these recommendations into effect forthwith.

Mr. VAN STRAUBENZEE asked for some categorical assurance to counteract the feeling that under the present administration at Broadmoor where there was a balance of doubt it was given to the patients rather than to those living in the neighbourhood. Mr. WALKER-SMITH: We do try to keep a fair balance between the interests of security, which are obviously important, and the interests of rehabilitation, which we also have to pursue under the duty cast on us by the Health Service. There had been outside working parties at Broadmoor for at least 40 years, and from 1941 to the end of 1959 there were only three escapes from working parties, none of them attended by any danger to the public.

Motorists' Safety-belts

Mrs. EIRENE WHITE (East Flint, Lab.) asked the Minister of Education on February 11, as representing the Minister for Science, what progress had been made in the investigations being carried out to show how many accidents might have been avoided had a safety-belt been worn by front-seat car passengers. Sir DAVID ECCLES stated that it was unlikely that accidents would be avoided by the wearing of a safety-belt by front-seat car passengers, but likely that the resulting injuries would be lessened. The Road Research Laboratory were attempting to obtain an estimate of the safety value of belts and harnesses by examining records of accidents which they had studied on the spot. An interim report was expected in a few weeks' time.

Noise Inquiry.—Mr. A. H. Wilson, F.R.S. is to be the chairman of the committee to consider noise and its effects. The membership of the committee has still to be completed.

Polio Vaccinations.—The Minister of Health is not aware of any deaths in England and Wales in 1959 ascribed to reactions following poliomyelitis vaccination.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

In Congregation on January 23 the following degrees were conferred:

M.D.—*W. Rodger, P. D. Griffiths, J. G. Bourne.
M.B., B.CHIR.—A. J. H. Nix.
M.B.—*J. Farmer, F. R. Gamman, D. Godwin, N. J. Barton, D. H. Keeling, *J. D. Allison, *T. S. Hattersley, C. J. F. Ll. Williamson, R. S. Kirk, *Mrs. Shirley J. Richmond.

*By proxy.

UNIVERSITY OF EDINBURGH

At a meeting of the University Court on January 25 Professor Emeritus D. E. C. Mekie, Director of Studies of the Edinburgh Postgraduate Board of Medicine, was admitted to the Faculty of Medicine.

Honorary status was conferred as follows: Honorary Lecturer in Forensic Psychiatry in the Department of Psychological Medicine, Dr. J. K. W. Morrice; honorary member of the clinical teaching staff in the department of Surgical Neurology, Dr. John Laidlaw.

The following were appointed members of the teaching staff: Dr. R. A. F. Murdoch, part-time Lecturer in Dental Surgery; Dr. E. S. Blackadder, part-time Lecturer in the General Practice Teaching Unit; and Dr. R. F. Robertson, to the clinical teaching staff in medicine.

Dr. N. L. Wright has resigned his appointment as assistant in the Department of Physiology and Dr. A. D. Forrest his appointment as Lecturer in Psychological Medicine.

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At the quarterly comitia of the College held on January 28, with the President, Sir Robert Platt, in the chair, Dr. E. R. Boland, Dr. T. C. Hunt, and Dr. J. B. Harman were reappointed as College representatives on the Central Medical Recruitment Committee for 1960–1; Dr. C. E. Newman was re-appointed as College representative on the Advisory Board on Nursing Education of the Royal College of Nursing for 1960–3; Lord Cohen of

Birkenhead was appointed as College representative on the Court of the University of Liverpool; Dr. H. S. Banks was appointed as College representative on the British Standards Institution; and Dr. G. E. Godber was appointed as College representative to the Health Congress of the Royal Society of Health to be held in Torquay from April 25 to 29, 1960.

The following candidates, having satisfied the Censors' Board, were elected Members of the College:

G. M. Ardran, M.D., J. Bamforth, M.B., M. A. Barraclough, M.B., J. R. Billinghurst, B.M., E. J. M. Bowlby, M.D., D. E. Christian, M.B., G. W. A. Dick, M.D., P. M. S. Gillam, M.B., M. Gross, M.B., D. D. Guttmann, B.M., R. M. McCredie, M.B., W. MacKenzie, M.D., A. B. Myles, M.B., K. A. K. North, M.B., H. L. Nossel, M.B., E. D. O'Callaghan, M.B., P. T. Pickens, B.M., M. S. Sabour, M.B., N. L. Schwartz, M.B., P. J. Scott, M.B., R. S. J. Simpson, M.B., J. H. Stewart, M.B., W. D. Stone, B.M., V. Thuraisingham, M.B., W. E. Watson, M.B.

Licences to practise were conferred upon the following 145 candidates who had passed the final examination in medicine, surgery, and midwifery of the Conjoint Board and who had complied with the by-laws of the College.

J. H. Ainsworth, E. G. Anderson, R. B. Andrews, R. I. A. A. Aubee, J. K. Bandoh, Sheila A. Beningfield, C. A. C. Bennett, R. P. Bishop, P. G. H. J. Bosley, Margaret J. Bown, Isobel J. N. Bradbury, J. S. Brewer, M. G. Brook, Diana C. Brown, J. P. B. Budgen, R. G. Bury, Janet R. Carruthers, M. E. Carruthers, F. Carter, Margaret E. Cash, Anne J. Cawthorne, M. J. Chamberlain, G. Champion, M. J. S. Coe, Bertha C. A. Coker, T. J. Colbridge, G. P. Coleman, Heather J. Collins, D. H. Coombe, A. S. Cooper, Linda F. Courtier, C. S. D. Crane, T. W. Darling, F. Dastur, H. R. Davies, J. G. Deller, E. R. Dixon, M. W. O. Dunwoody, Kathleen J. B. Edwards, E. I. Efiong, Mary Ellis, M. W. Farrar, J. T. L. C. Fernando, A. E. Finnigan, D. J. Fishlock, P. R. Goddard, A. B. Griffiths, J. B. Gritton, J. H. Hackwood, Edna Hallam, D. R. Harvey, I. B. Hayter, Ann Henley, Pauline B. Hird, K. E. F. Hobbs, R. C. Hodge, G. T. Hollingworth, A. S. Horner, P. Howard, E. G. Hoyen-Chung, K. E. E. Hubble, M. K. G. Hudson, W. F. G. Hulley, M. J. Hunter, R.-K. R. Innes, P. Jackson, C. W. Jamieson, Rosemary Khin Zaw, R. S. Kirk, Elizabeth S. Kitchin, C. C. Korvin, A. P. Lees, Eva Lester, C. C. Lim, J. D. Lloyd-Still, S. J. McDonald, S. McHardy-Young, Marion McLellan, Margaret R. McMinn, Margaret M. McNamara, J. J. M. Marot, June E. Marrable, Harriet M. C. Mason, Pamela J. Massie, R. E. May, R. D. G. Milner, R. L. Mitchell, M. Modell, M. A. Modelski, J. F. Moore, T. S. Morley, A. E. Morris, M. D. R. Morris, J. F. Murray, A. J. H. Nix, J. R. Norman, G. Nuki, D. A. Ogbe, P. M. Olley, E. G. J. Olsen, S. M. Patient, H. G. Peters, J. B. Phillips, D. Pickering, C. I. Porter, A. R. C. Ralph, D. Ramprotal, L. M. Razavi, R. J. Rew, D. A. Reynolds, M. T. Reynolds, Janet Riddle, A. D. Rogers, P. J. Y. Scott, P. Sharpstone, C. M. Signy, G. M. Slade, J. K. Smallshaw, M. J. Smith, A. O. O. Sorungbe, F. B. Stephenson, Mary Stewart, A. E. Stocks, Norma A. Taylor, R. G. N. Thomson, R. Tiru-Chelvam, P. M. J. Tombleson, M. Ugwunze, K. Urwin, P. L. H. Vernon, B. A. Waldron, Judith G. Walker, B. A. Wallace, P. J. Watt, Tessa Westcott, Myra Wharf, W. F. White, R. W. Wille, D. E. Williams, J. G. Williams, N. Williamson, J. G. Wingfield, M. S. Wirk, J. D. Wonham, Adeline C. L. Yen.

Diplomas in Laryngology and Otology, in Medical Radiodiagnosis, in Medical Radiotherapy, in Pathology, in Public Health, and in Tropical Medicine and Hygiene were granted, jointly with the Royal College of Surgeons of England, to the successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of January 30 (p. 358).

Diplomas in Anaesthetics were granted, jointly with the Royal College of Surgeons of England, to G. Chasapakis and to the other successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of January 30 (p. 358).

Diplomas in Psychological Medicine were granted, jointly with the Royal College of Surgeons of England, to A. K. M. N. Chowdhury and to the other successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of January 30 (p. 358).

The following diplomas were granted, jointly with the Royal College of Surgeons of England:

DIPLOMA IN CHILD HEALTH.—E. G. Mendis, R. N. Mukerjee.
DIPLOMA IN INDUSTRIAL HEALTH.—F. K. Amroliwalla, J. C. Cape, J. C. Chakrabarti, Catherine J. S. Gauvain, P. A. Lee, Z. Lukic, I. A. McIntosh, Vlasta Mucic, J. H. Neal, A. R. N. Prasad, R. C. Robb, E. R. Simpson, Rosemary Trewby.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on January 30, with the President in the chair, the following candidates were elected to the Membership:

A. A. Anklesaria, Alison M. Armstrong, M. P. Awon, A. Banerjee, J. D. Begg, K. K. O. Bentsi-Enchill, K. G. Bland, Kathleen A. S. Brosnan, G. R. Brown, S. Burgin, B. K. Chakrabarti, S. Chakravorty, F. R. Clark, H. Cohen, J. B. Comerford, F. G. Cox, Gerda J. Crow, M. M. de la Harpe, R. A. Don, Sheila L. B. Duncan, S. Ende, P. H. Foote, A. C. Fraser, K. E. Free, I. K. Furler, W. T. Gallagher, Susan George, R. Giles, C. S. Harison, P. D. Hill, U. Jacobson, S. B. Kamath, P. S. Kan, S. Kataria, B. Keane, B. C. Lahiri, A. B. N. Marzuki, T. N. Mitra, T. K.-F. Ng, D. B. Paintin, Heather M. Panton, Mary C. W. Paterson, E. C. Pixley, G. Ll. S. Rankin, L. J. Schewitz, S. C. Simmons, N. J. Talati, E. P. W. Tatford, Moliy E. Towell, Mary M. Tyndall, R. J. Venn, N. F. Walker, W. A. W. Walters, D. K. Williams, L. H. Wright.

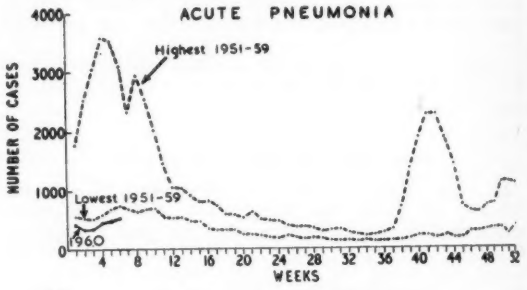
Vital Statistics

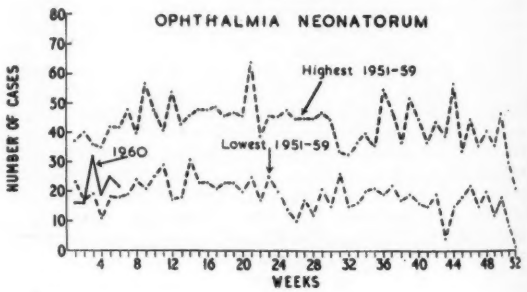
Influenza in England and Wales

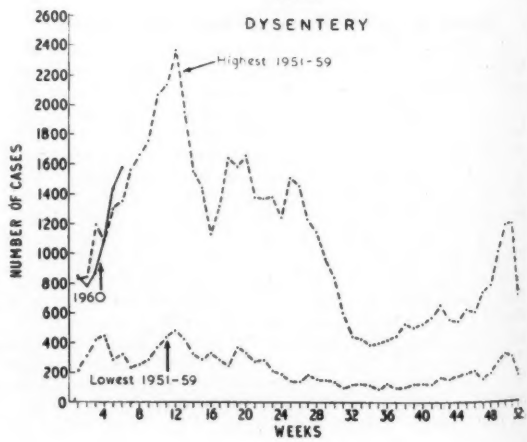
During the week ending February 13 the notifications of pneumonia (505) and the deaths from pneumonia (657), bronchitis (705), and influenza (38) were all close to the figures recorded during the past few weeks and much lower than those recorded the same week last year. During the week ending February 9 there were 185,791 new claims on the Ministry of Pensions and National Insurance (compared with 299,574 a year ago) and 1,210 applications for a hospital bed to the London Emergency Bed Service (compared with 1,730 applications a year ago).

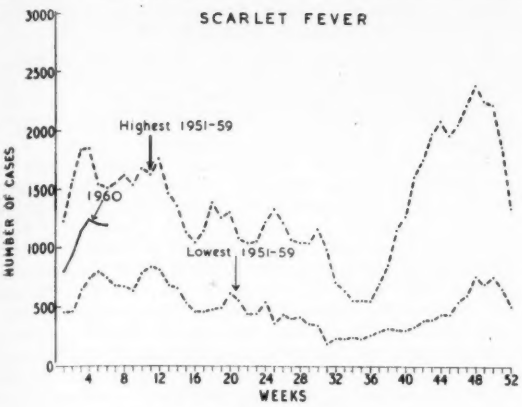
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus -----, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Feb. 6	Feb. 13
Diphtheria		
Essex	1	**4**
Walthamstow M.B.	1	**4**
Dysentery		
Dorsetshire	49	**22**
Portland U.D.	40	**18**
Durham	11	**54**
Sunderland C.B.	0	**14**
Essex	51	**76**
Saffron Walden M.B.	10	**35**
Saffron Walden R.D.	1	**12**
Lancashire	330	**413**
Bolton C.B.	43	**30**
Liverpool C.B.	41	**48**
Manchester C.B.	5	**18**
Oldham C.B.	66	**50**
Preston C.B.	22	**38**
Ashton-under-Lyne M.B.	0	**33**
Prestwick M.B.	0	**12**
Royton U.D.	7	**15**
Swinton and Pendlebury M.B.	16	**43**
Lincolnshire	28	**33**
North Kesteven R.D.	22	**13**
Louth M.B.	0	**10**
London	155	**220**
Camberwell	12	**15**
Islington	10	**26**
Lambeth	8	**24**
St. Pancras	3	**10**
Southwark	55	**48**
Wandsworth	16	**16**
Middlesex	76	**89**
Edmonton M.B.	45	**45**
Enfield M.B.	5	**16**
Surrey	46	**83**
Barnes M.B.	0	**12**
Carshalton U.D.	7	**39**
Caterham and Warlingham U.D.	2	**17**
Yorkshire North Riding	12	**20**
Redcar M.B.	9	**17**
Yorkshire West Riding	109	**93**
Bradford C.B.	6	**25**
Leeds C.B.	14	**14**
Sheffield C.B.	22	**20**
Glasgow	144	**155**
Food-poisoning		
Yorkshire West Riding	7	**117**
Settle R.D.	0	**110**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 6** (No. 5) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	2	0	2	0	9	2	0	3	0	
Dysentery	1,433	155	260	2	3	1,294	92	127	13	9
Encephalitis, acute	0	0		0		2	1		0	
Enteric fever:										
Typhoid	1	1	0	0		0	0	0	0	
Paratyphoid	0	0	1(B)	0		10	1	0	0	
Food-poisoning	177	43	34	2		129	13	4	0	
Infective enteritis or diarrhoea under 2 years				7	23				16	40
Measles*	1,580	44	26	12	6	22,170	1438	630	330	944
Meningococcal infection	30	5	7	0	1	28	7	13	2	3
Ophthalmia neonatorum	25	4	4	0		29	4	4	0	
Pneumonia†	467	30	249	4	2	943	90	563	8	4
Poliomyelitis, acute:										
Paralytic	4	2	0	0	3	12	0	1	0	2
Non-paralytic	1	0	1			6	0	1		
Puerperal fever§	213	28	4	1	1	218	37	9	0	
Scarlet fever	1,208	51	100	27	20	1,389	75	63	35	38
Tuberculosis:										
Respiratory	440	48	71	17		504	65	85	14	
Non-respiratory	47	2	10	6		47	2	11	4	
Whooping-cough	1,037	74	196	13	97	758	26	45	87	177

DEATHS	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		2	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	15	33	0	0	0	6	0	0	0	0
Influenza	36	2	2	0	0	144	10	12	0	0
Measles		0	0	0	0		1	1	0	0
Meningococcal infection		0	1				1	0		
Pneumonia	682	68	34	29	11	986	95	66	21	8
Poliomyelitis, acute	0	0		0	0	2	1		0	0
Scarlet fever	1,208	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	79	3	13	0	2	123	9	15	0	9
Non-respiratory		0	0	0	0		0	1	0	1
Whooping-cough	1	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	341	33	29	9	15	354	37	38	5	11
Deaths (excluding stillbirths)	11,176	912	690	136	173	13,692	1241	996	160	188
LIVE BIRTHS	14,977	1276	1050	271	383	14,692	1245	939	254	384
STILLBIRTHS	325	42	19			341	34	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Rockefeller Foundation Grants

During the last three months of 1959 the Rockefeller Foundation made grants totalling $12,398,008, $5,855,385 of which was absorbed by the medical and natural sciences.

In the United Kingdom, Churchill College, Cambridge, and St. Catherine's College, Oxford—both established largely to provide facilities in the natural sciences and mathematics—have been given $100,000 (about £35,700) each over the next five years for a Visiting Fellows programme. The London School of Hygiene and Tropical Medicine's research in combating protein malnutrition in underdeveloped areas has been assisted by a three-year appropriation of £24,000. Individual grants have been made to Dr. J. E. MACIVER (senior lecturer in haematology, faculty of medicine, University College of the West Indies, Jamaica) to assist in haematological research and in organizing a haematological service at the faculty of medicine, University of Caldas, Manizales, Colombia; to Professor E. M. BACKETT (professor of public health and social medicine, Aberdeen University) for visiting centres of medical education and epidemiology in the United States; and to Professor RUTH E. M. BOWDEN (professor of anatomy, Royal Free Hospital School of Medicine) to study medical education and procedures at medical schools while in America. A Fellowship on behalf of the Medical Research Council has been awarded to Mr. H. L. DUTHIE (lecturer in surgery, Glasgow University) for study in America. In America itself a grant of $3m. has been made to the Stanford University school of medicine to finance its major reorganization and development programme. Among those appointed to the university's recently established full-time professorships are two Nobel prize winners—Dr. A. KORNBORG (biochemistry) and Dr. J. LEDERBERG (medical genetics).

Radiotherapeutics at Manchester University

Dr. JAMES RALSTON KENNEDY PATERSON has been granted the status of professor, with the title of professor of radiotherapeutics at the University of Manchester from March 1. He is at present lecturer in clinical radiotherapy. He will continue to hold his appointment as director of radiotherapy at the Christie Hospital and Holt Radium Institute, Manchester.

Mr. Paterson proceeded from George Heriot's School, Edinburgh, to the University of Edinburgh Medical School, where he graduated with honours in 1923. He then went to Cambridge and studied for the D.M.R.E. which he obtained in 1924. He became F.R.C.S.Edin., in 1926 and was awarded the degree of M.D. with commendation in 1927. From 1926 to 1930 Dr. Paterson held appointments in Minnesota and Chicago. In 1930 he was appointed acting director of the radiological department in the Edinburgh Royal Infirmary and from that post came to Manchester in 1931 to take up his present appointment. In 1953 he became honorary director of the Medical Research Council's Betatron Research Unit. The Royal College of Surgeons of England made him an Honorary Fellow in 1948 and he was made a C.B.E. in 1950. Dr. Paterson has served on many national and international committees dealing with the treatment of cancer by radiotherapy and has travelled widely on official advisory visits on cancer and radiotherapy services. He is the author of a textbook on *Treatment of Malignant Disease by Radium and X-rays*.

Industrial Health Advisory Service for the North

A new North of England Industrial Health Advisory Service covering Northumberland, Cumberland, County Durham, and the North Riding of Yorkshire has just been established. A consultant team from the medical department of industrial health, King's College, Newcastle upon Tyne, will be available to advise the Service in its early stages. The honorary director is Professor R. C. BROWNE (Nuffield department of industrial health, King's College); the honorary secretary Dr. R. I. MCCALLUM (senior lecturer in the department); and the committee of management includes Professor R. B. GREEN (dean of medicine, King's College). Full details may be obtained from the Honorary Director, North of England Industrial Health Advisory Service, 52, Leazes Terrace, Newcastle upon Tyne, 1.

The Nuffield Provincial Hospitals Trust has made the Service an initial capital grant of £11,500, and £3,000 was added from the King's College Students' Rag Appeal Fund, 1957. The provisional cost to firms will be 2s. a head of the number employed.

Postgraduate Medical School Reception

A reception at the Postgraduate Medical School of London was held on February 17 by its President, Field-Marshal EARL ALEXANDER OF TUNIS, and the chairman of the management committee, LORD COLERAINE. Lord Alexander expressed the gratitude of the School for the financial help it had received from the Commonwealth, whence many of its students came. In particular, Pakistan had made a fine gesture by starting with a gift of £1,000, and South Africa had already given £37,000. Canada intended to make a donation now that certain tax laws had been changed there. Lord Coleraine also thanked the School's benefactors, including Mr. Isaac Wolfson.

Among the guests were Professor NORMAN ASHTON, Brigadier Sir JOHN BOYD, Sir JOHN CHARLES, Sir ANDREW CLAYE, P.R.C.O.G., Sir HENRY DALE, O.M., Lord EVANS, Sir FRANCIS FRASER, Dr. CHARLES HILL, Lord HOME, Sir AUBREY LEWIS, Professor W. MELVILLE ARNOTT, Madam PANDIT, Mr. ISAAC WOLFSON, and Professor JAMES YOUNG.

Horder Travelling Fellowship

It is hoped that funds from the Horder Memorial Trust will enable a senior member of the medical profession to undertake a travelling Fellowship in 1961—preferably in the Commonwealth countries—and every three years thereafter. The trustees will be drawn partly from the Royal College of Physicians and partly from St. Bartholomew's Hospital, the selected candidate being asked to lecture in one or other of these institutions. The Fellowship will not be advertised, but a selection committee will be appointed early in October. The Trust's secretary is Dr. E. M. DARMADY, Central Laboratory, Milton Road, Portsmouth.

"British Medical Students' Journal"

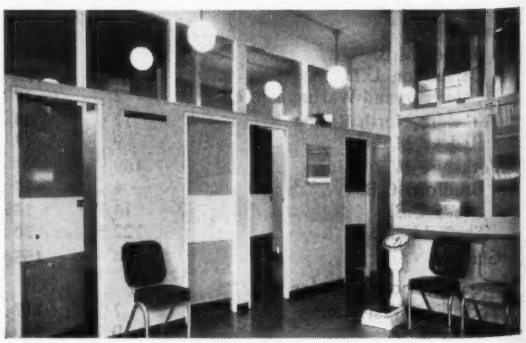
Medical students usually have the reputation of being more ribald than serious, but the January issue of *B.M.S.J.* includes a thoughtful leader on World Refugee Year, and news of an appeal for textbooks for refugees, saying that these are consumed so avidly that one might suppose they satisfied their ever-present physical hunger.

The issue contains articles on visits to Canada, to America, and to Russia ("Ah Angliski . . . David Copperfield . . ."). For the impecunious there are details of a photographic competition and rewards for cover designs, and for the adventurous an S.O.S. for a sixth man to film a Cambridge expedition covering the route of the first crusade and visiting some virtually unknown crusader castles. The *B.M.S.J.* costs 6d. to members of the B.M.S.A., and 1s. to non-members, plus postage, from B.M.S.A., B.M.A. House, Tavistock Square, London, W.C.1.

New Obstetric Unit at Charing Cross Hospital

The new obstetric unit at Charing Cross Hospital was inaugurated on February 23 by Sir ANDREW CLAYE, P.R.C.O.G.

Sir Andrew, who was introduced by Professor W. J. HAMILTON, dean of the medical school, spoke on the function of an academic



obstetric unit, and produced, in passing, an attractive translation of Horace's "*Vixere fortes ante Agamemnona multi*"—"A lot of good work was done before ever there were full-time chairs." The aim of the new unit, as Professor NORMAN MORRIS made clear in his inaugural speech, was to create a relaxed and cheerful atmosphere; this was infinitely easier in the colourful surroundings of the new unit than in the one it replaced, which might, not unfairly, be described as "classical early Victorian." A vote of thanks was moved by Mr. H. G. E. ARTHURE, senior obstetrician and gynaecologist. For about £15,000—and without reducing the original number of 30 beds—a modern unit with many new facilities has been provided, including the gaily painted antenatal clinic shown here.

Preserving Medical Records

The British Records Association has published a memorandum (No. 16) on *Preservation of Medical Records* (*Lancet*, February 13, p. 379), copies of which can be obtained free from the secretary, Records Preservation Section, British Records Association, The Charterhouse, London, E.C.1. A convenient statement of more general principles for the disposal of records can be found in another association memorandum (No. 7), *Modern Records, What May We Destroy?*

Conference on Congenital Malformations

The first international conference on congenital malformations will take place in London from July 18 to 22, under the honorary presidency of Mr. BASIL O'CONNOR and Sir GEOFFREY MARSHALL. Professor J. D. BOYD, professor of anatomy at Cambridge University, will be the general chairman.

There will be eight scientific sessions during the conference, on incidence; intrinsic factors (genetics); extrinsic factors (environment); general developmental mechanisms; abnormal developmental mechanisms; maternal foetal interactions; physiological and medical problems; and perspectives. Details may be obtained from the Secretariat of the Conference on Congenital Malformations, 67, New Bond Street (Dering Yard), London, W.1.

Toxic Chemicals in Agriculture

Among those who will serve on the research study group to examine the use of toxic sprays in agriculture are Dr. J. M. BARNES, Dr. DONALD HUNTER, and Professor W. L. M. PERRY.

World Mental Health Year

Mr. KENNETH ROBINSON, M.P., has accepted the Bruern Foundation Travelling Fellowship given in connexion with World Mental Health Year. He is to study mental health services in other countries in relation to those in the United Kingdom.

Weizmann Institute of Science Research Chair

Mr. JACK COTTON has endowed a research chair at the Weizmann Institute of Science in Israel with a gift of £70,000.

The Jack Cotton Chair will be in the Institute's experimental biology department which carries out research in cancer, endocrinology and reproductive physiology, and radiation hazards.

"Family Doctor"

The March issue of *Family Doctor* is now available, price 1s. 6d. It includes articles on caesarean section, by Mr. ELLIOT PHILIPP, and varicose veins, by Dr. S. RIVLIN.

COMING EVENTS

Oliver-Sharpey Lectures.—Dr. J. D. N. NABARRO: "The Pituitary and Adrenal Cortex in General Medicine." For details see *Journal* advertisement p. 70.

Institute of Dermatology.—Semi-permanent exhibitions are available during the winter term: March 3–30, "Treatment of Basal-celled Carcinoma" by Mr. R. J. Battle.

Institute of Basic Medical Sciences.—Course in genetics, statistics, and radio-isotopes, March 14–16. Details from Mr. W. F. DAVIS, Institute of Basic Medical Sciences, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2. (HOLborn 3474.)

Nutrition Society.—Symposium: "Nutrition and the Elderly." Medical College of St. Bartholomew's Hospital, Charterhouse Square, London, E.C.1, 9.45 a.m., March 19. Details from Miss D. F. HOLLINGSWORTH, c/o Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London, S.W.1.

Dental Implant Society.—Dr. GEORGE F. EGAN (oral surgeon, New York Hospital), lecture and film, March 23, 7.30 p.m., 1, Wimpole Street, London, W.1. Details from the Society, 109, Harley Street, London, W.1.

Ophthalmological Society of United Kingdom.—80th annual congress, March 31–April 2, Royal Society of Medicine, 1, Wimpole Street, London, W.1. Details from the Ophthalmological Society's Secretary, 47, Lincoln's Inn Fields, London, W.C.2.

Refresher Course for General Practitioners.—Joyce Green Hospital, Dartford, Kent, 3 p.m. each Friday, from April 22 to July 1 inclusive. Inquiries to Dr. J. C. HOGARTH, West Hill Hospital, Dartford, Kent.

67th Annual Congress, Royal Society of Health.—Torquay, April 25–29. For the first time a section will be devoted to the Executive Councils Services. Other subjects will be mental health, health education, preventive medicine, family health and welfare, occupational health, world health, and hospitals. Details from the Society, 90, Buckingham Palace Road, London, S.W.1.

10th Psychotherapeutic Week. — Lindau (Bodensee), Germany, May 2–14, in association with the Allgemeine Ärztliche Gesellschaft für Psychotherapie. President: Dr. HELMUTH STOLZE. Details from the Secretariat, Lindauer Psychotherapiewoche, 17, Dienerstrasse, Munich, 2, Germany.

William Withering Lectures.—Professor J. Z. YOUNG: "Mechanisms of Learning and Form Discrimination." May 2, 3, 4, at 5 p.m., Medical School, Birmingham University, Birmingham, 15.

Ingleby Lectures.—Professor Sir DUGALD BAIRD: "The Evolution of Modern Obstetrics." May 18–19, 5 p.m., Medical School, Birmingham University, Birmingham, 15.

Symposium on Fungus Infection.—Symposium: "Oral Treatment of Fungus Infections with Griseofulvin." Royal Society of Medicine, May 13–14, with sessions on histological, clinical, and pathological aspects. Details from the Secretary of the Symposium, St. John's Hospital Dermatological Society, St. John's Hospital, 5, Lisle Street, London, W.C.2.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.*1.

British Heart Journal.—Issued quarterly (£3 annually). The new issue (Vol. 22, No. 1) includes:

The Heart in Systemic Lupus Erythematosus. W. Brigden, E. G. L. Bywaters, M. H. Lessof, and I. P. Ross.

The Aetiology of Systemic Hypertension. William Evans.

The Interpretation of Pulmonary Artery Wedge (Pulmonary Capillary) Pressures. W. H. Bernstein, E. M. Fierer, M. H. Laszlo, P. Samet, and R. S. Litwak.

Coronary Heart Disease in Seven Racial Groups in Singapore. C. S. Muir.

Cine-angiography of the Coronary Circulation in Living Dogs. Graeme Sloman and Keith Jefferson.

Vectorcardiography in Myocardial Infarction. G. Howitt and T. D. V. Lawrie.

A Sensitive and Stable Earpiece for Dye Dilution Curves. John Norman.

The Anoxia Test for Myocardial Ischaemia. Norman Coulshed.

Ebstein's Syndrome. K. P. Sinha, J. F. Uricchio, and H. Goldberg.

Relationship of Pressure and Valve Area in Pulmonary Stenosis. Maurice Campbell.

The Kinked Innominate Vein. K. Shirley Smith.

Circulatory Studies at Rest and During Exercise in Coarctation of the Aorta Before and After Operation. S. H. Taylor and K. W. Donald.

Rheography. K. Polzer, F. Schuhfried, and H. Heeger.

Case Report

Gummatous Myocarditis. W. Leach.

Journal of Neurology, Neurosurgery, and Psychiatry.—Issued quarterly (£3 annually). The new issue (Vol. 22, No. 4) includes:

Some Observations on the Pathogenesis and Natural History of Intracranial Aneurysms. T. Crawford.
Some Sensory Syndromes in Children: Indifference to Pain and Sensory Neuropathy. T. E. Ogden, Francoise Robert, and E. Arnold Carmichael.
The Non-specificity of the Intrathecal Reaction to Tuberculin in Multiple Sclerosis. John Marshall and Francis O'Grady.
The Seasonal Incidence of Onset and Exacerbations in Multiple Sclerosis. Kurt Schapira.
The Significance in Human Stereotactic Brain Surgery of Individual Variation in the Diencephalon and Globus Pallidus. J. B. Brierley and Elisabeth Beck.
Sensory, Motor, and Reflex Changes in Two Cases of Intractable Pain after Stereotactic Mesencephalic Tractotomy. Ansgar Torvik.
Quantitative Electromyographic Changes Associated with Muscular Weakness. J. A. R. Lenman.
The Diaphragm in Dystrophia Myotonica. J. E. Caughey and N. Pachomov.
Myopathy in Cushing's Syndrome. Ragnar Müller and Eric Kugelberg.
Some Muscular Manifestations of Hypothyroidism. John Wilson and John N. Walton.
Histochemical Distribution of Phosphorylase in the Brain of the Guinea-pig. Reinhard L. Friede.
Congenital Intraorbital Arteriovenous Aneurysm. Ramón Jacas, Adolfo Ley, and Domingo Campillo.
Neurological Changes with Intracarotid Amytal and Megimide in Man. Robert Werman, Nicholas Christoff, and Paul J. Anderson.
The Prognosis for Affective Illness with Overt Anxiety. Lindsay Walker.

Annals of the Rheumatic Diseases.—Issued quarterly (£3 annually). The new issue (Vol. 18, No. 4) includes:

Familial Incidence of Rheumatoid Arthritis. Joan M. Bremner, W. R. M. Alexander, and J. J. R. Duthie.
Acute Rheumatic Fever in Young Men. J. D. H. Slater and S. Rosenbaum.
Differences Between the Fever of Still's Disease and that of Rheumatic Fever. F. J. McMinn and E. G. L. Bywaters.
Salicylates and the Adrenal Cortex. M. J. H. Smith.
Experience with British Latex Suspension for Agglutination Tests in Rheumatoid Arthritis. Harry Coke.
Evaluation of an Epidemiological Method. Stephen E. Malawista, Lawrence R. Boies, and S. Warren Seides.
Anti-Inflammatory Effect of Obstructive Jaundice in Rats. Ronald L. Engerman and Roland K. Meyer.
Urinary Indoles and other "Ehrlich's Reagent Reactors" in Rheumatoid Arthritis. Martti Oka and V. V. E. Leppänen.
Importance of an Increased Gamma Globulin Level in the Determination of Gm Groups in Collagen Diseases. H. Julkunen and Anja Tiilikainen.
Comparative Study of the Haemagglutination Test and a Simple Latex-Fixation Test for the Detection of the Rheumatoid Factor. G. Morgan.
Comparison of Intra-Articular Cortisone Analogues in Osteo-Arthritis of the Knee. M. J. Kehr.
Book Review.
Canadian Rheumatism Association.
Heberden Society.
Ligue Européenne contre le Rhumatisme
Abstracts
Index.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription, £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 29

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Modern Drug Treatment of Mental Disorder.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. Antoinette Pirie: Biochemistry of the Eye.

Tuesday, March 1

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. A. Isaacs: Anti-viral Action of Interferon.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. I. Muende: Diagnosis and Treatment of Fungous Infections.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Mr. Wylie McKissock: Surgical versus Medical Treatment of Posterior Communicating Aneurysm.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Lecture Theatre, 5 p.m., Mr. C. W. F. Burnett: Some Aspects of Abortion.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. K. I. Nissen: Mechanism and Treatment of Compression of the Median Nerve at the Wrist.

Wednesday, March 2

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Mr. T. E. Hughes: Mites or Acari.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. W. P. Cleland: Surgical Treatment of Fallot's Tetralogy.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. D. I. Williams, Congenital Defects of the Genital Tract.
●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, 8 p.m., Dr. W. H. Taylor: Metabolic Disorders Associated with Diseases of the Nervous System.
LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., special university lecture in pathology, by Professor Gerhard Schramm (Tübingen): Mutagenesis in Viruses.
MIDLAND MEDICAL SOCIETY.—8.15 p.m., Dr. Douglas Hubble: Growth and its Disorders.
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Dr. D. Denny-Brown: Nature of Brief Recurrent Cerebrovascular Episodes.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. J. A. Fraser Roberts: Sex-linked Inheritance in Man (III).
SOCIETY FOR ANALYTICAL CHEMISTRY.—At Queen's Hotel, Stephenson Place, Birmingham, 4.30 p.m., annual general meeting; 5 p.m., Bernard Dyer Memorial Lecture by Professor A. C. Frazer: Contribution of Analytical Chemistry to Medical Progress; 7 for 7.30 p.m., informal dinner.

Thursday, March 3

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., visit of Manchester Medical Society.
NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Dr. W. H. Harris: Fibrous Dysplasia.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Otolaryngology Lecture by Dr. R. M. B. MacKenna: Dermatological Aspect of Certain of the Diseases of the Mouth and Ear.

Friday, March 4

ABERDEEN UNIVERSITY: DEPARTMENT OF SURGERY.—At Medical School, Foresterhill, 5 p.m., Mr. L. P. LeQuesne: Postgastrectomy Dumping Syndromes.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. J. Hare: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Dr. D. A. Osborn: Blood Diseases in Ear, Nose, and Throat Conditions.
INSTITUTE OF NEUROLOGY.—4.30 p.m., Dr. Macdonald Critchley: The History of Our Conception as to the Origins of Language in Man (Part II).
METROPOLITAN EAR, NOSE, AND THROAT HOSPITAL.—At Royal Society of Medicine, 5 p.m., 6th Annual James Yearsley Memorial Lecture by Mr. Ian Thorburn: Critical Review of Tympanoplastic Surgery.
MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane, Smethwick, near Birmingham.—8 p.m., Professor D. Denny-Brown: Nature of Polymyositis and Related Muscular Disease.
PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., Dr. T. F. Fox: The Art of the Article.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Sir Eric Riches: New Growths of the Kidney. (2) 4 p.m., Dr. J. A. Fraser Roberts, Medical Genetics (IV).

Saturday, March 5

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, Symposium on Anaesthesia for the Aged. 10.30 a.m., Dr. W. Davison: The Pre-anaesthetic Assessment of Aged Patients; 11.45 a.m., Dr. John Beard: Anaesthesia for the aged; 2.30 p.m., D. M. W. Johnstone: Halothane as an Anaesthetic for Aged Patients; 3.30 p.m., Dr. H. R. Youngman: Epidural Analgesia for Aged Patients.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—12 noon, Professor Michel Portman (Bordeaux): Interposition for Otosclerosis.
MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 3 p.m., Sir Clement Price Thomas: Mediastinal Abnormalities and their Treatment.

Sunday, March 6

UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main Hospital. Lecture-demonstration for general practitioners. Dr. D. A. Pond: New Stimulants and Tranquillizers in Psychiatry.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—O. E. F. Hodgson, M.B., B.Chir., D.P.M., Consultant Psychiatrist, Fulbourn and Addenbrooke's Hospitals; J. A. Dew-Jones, M.R.C.S., L.R.C.P., Senior Registrar in Psychiatry, St. Andrew's Hospital, Norwich; Jane G. Jenkinson, M.B., B.S., D.C.H., Paediatric Registrar, Ipswich and East Suffolk Hospital; B. A. M. Smith, M.B., Ch.B., D.C.H., Paediatric Registrar, Peterborough Group of Hospitals; N. A. Jadhav, M.B., B.S., M.R.C.P.Ed., Medical Registrar, North Cambridgeshire and Clarkson Hospitals, Wisbech; A. W. Skorbinski, M.B., Ch.B., Surgical Registrar, Peterborough Memorial Hospital; W. G. Harris, M.B., B.S., Surgical Registrar, Ipswich and East Suffolk Hospital; G. A. Lawrence, M.B., B.S., F.R.C.S.Ed., Surgical Registrar, Norfolk and Norwich Hospital; S. P. Singh, M.B., B.S., M.R.C.P.Ed., Medical Registrar, West Suffolk General Hospital; I. P. Sukumar, M.B., B.S., Medical Registrar, Papworth Hospital; R. V. Boyd, M.B., B.S., D.C.H., Registrar in Geriatrics, Ipswich and East Suffolk Hospital Group.

BIRTHS, MARRIAGES, AND DEATHS

MARRIAGES

Hawley—Vartan.—On February 6, 1960, at Priory Church of St. Bartholomew the Great, London, E.C., Richard Trevor Hawley, M.B., B.S., to Hilary Mitchell Vartan.
Johnstone—Godden.—On February 20, 1960, at West Wickham, Kent, Frederick C. Johnstone, B.M., B.Ch., to Miss Sheila Godden, M.S.C.P. (Physiotherapy), of Beckenham.

DEATHS

Boyd.—On January 29, 1960, at Eastbourne, Wellington, New Zealand, James Roberts Boyd, C.B.E., *M.C.*, M.D., F.R.C.P.Ed.
Campbell.—On January 29, 1960, Alexander David Campbell, M.B., Ch.B., D.P.H.
Grant.—On January 25, 1960, Willoughby Gordon Grant, M.R.C.S., L.R.C.P., of Margherita, Assam, and Ootacamund, South India.
Hill.—On January 27, 1960, Arthur Kennedy Hill, M.B., Ch.B., D.I.H., of 106, Portland Road, Edgbaston, Birmingham.
McDonald.—At Chislehurst, Kent, Charles Knight McDonald, M.D., D.P.H.Ed.
Macfiggans.—On January 24, 1960, at Nairobi, Kenya, Robert Macfiggans, M.B., Ch.B.
Mulock-Bentley.—At Princess Alice Avenue, Durban, South Africa, Thomas Mulock-Bentley, M.B., aged 93.
Powell.—On January 22, 1960, at his home, "Marnis," Copse Mead, Woodley, near Reading, Leslie Powell, M.B., B.Ch., aged 76.
Woolham.—On January 28, 1960, at Windsor Hospital, Josiah Gilbert Woolham, M.D., D.P.H.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Cerebral Arterial Spasm

Q.—*Is there such a thing as cerebral arterial spasm? How can it be diagnosed and treated?*

A.—This is a controversial subject. It is quite clear that spasm of cerebral arteries can occur following subarachnoid haemorrhage from an intracranial aneurism, since in cases of this type it has been demonstrated by angiography and at craniotomy. Cerebral arterial spasm is usually considered to be the cause of the visual and sensory aura which may occur in migraine; there is no absolute proof of this, but the explanation seems likely, and in some patients the aura may be much more prominent than the headache or may even occur without a headache. The other type of case in which spasm of cerebral arteries has been suggested is the patient, often with arterial hypertension or evidence of cerebral arteriosclerosis, who has repeated transient disturbances of cerebral function—for example, hemiplegia or aphasia. In some of these patients angiography will demonstrate thrombosis or stenosis of one internal carotid artery, and similar changes can also occur in the vertebral basilar system. In other patients, however, with transient attacks of hemiplegia, angiography may not show any convincing evidence of structural disease of carotid or cerebral arteries, and it is possible, but unproved, that cerebral arterial spasm is the cause of the transient disturbances.

Desensitization to Streptomycin

Q.—*Is it possible to desensitize a patient who had a reaction after being given streptomycin and dihydrostreptomycin systemically?*

A.—Desensitization to streptomycin and dihydrostreptomycin is possible.[1–6] Before doing it, however, it is necessary to prove hypersensitivity and to find its level by skin-testing. Dihydrostreptomycin is less likely to cause hypersensitivity reactions than is streptomycin.[2]

In patients very allergic to streptomycin, such as nurses or dispensers hypersensitive by contact, skin-testing should start with 10 μg.; if the result is negative, then with 100 μg.; then 1 mg., and, if still negative, 10 mg.[3] In patients, such as tuberculous patients, who develop sensitivity during treatment, intradermal testing with 10 mg. is advised.[4] The skin reaction is of a delayed type which becomes positive in 12–24 hours. A positive reaction gives an area of induration of 5 mm. or more, and when the test is negative there is only erythema and no induration.

Desensitization starts with a test dose just below that which gives a positive reaction, and, in the absence of any reaction, the dose is subsequently doubled each time and given daily or on alternate days. Mild reactions indicate a need for repeating the same dose, and severe reactions a need for lowering the dose and a subsequent more gradual increase. Antihistamines can be given as a cover to lessen the tendency to reactions. Cohen,[3] in the case of a ward-sister, used doses of 0.5 mg., 1 mg., 2 mg., 5 mg., 10 mg., 50 mg., 100 mg., 200 mg., and 500 mg., 1 g., and 1 g., with promethazine hydrochloride as a cover. Livingstone[4] described desensitization, with chlorcyclizine as a cover, as relatively easy in most patients sensitized by treatment. He advised that the drug should be stopped for 7 or 10 days to allow the rash or other manifestation to clear before starting desensitization. He reported a common starting dose of 0.1 g. followed by 0.15, 0.2, 0.25, 0.3, 0.4, 0.5, 0.6, 0.8, and 1 g.

Pines[5] desensitized under prednisolone cover a nurse who had become sensitized to streptomycin from handling, and Chakravarty[6] used prednisone as a cover in patients who had been sensitized during treatment. He gave prednisone 50 mg. orally daily for one week after a positive skin-test with 10 mg. of streptomycin, and then the skin-test was repeated. Usually it was negative, but if it was still positive prednisone was given for another week. Desensitization under prednisone began with streptomycin 10 mg., and the dose was doubled daily up to 800 mg. Then 1 g. was given twice weekly, and after four weeks the prednisone was tapered off and stopped in about two weeks. Before stopping prednisone, 20 units of A.C.T.H. was given daily and tapered off in two weeks. Desensitization was satisfactory in all the cases.

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1 Crofton, J., *Brit. med. J.*, 1953, **2**, 1014.
2 Goodman, L. S., and Gilman, A., *Pharmacological Basis of Therapeutics*, 1955, 2nd ed., p. 1370. Macmillan, New York.
3 Cohen, R. C., *Tubercle*, 1954, **35**, 142.
4 Chakravarty, S., *Dis. Chest*, 1957, **32**, 310.
5 Pines, A., *Brit. med. J.*, 1957, **2**, 202.
6 Livingstone, J. L., *Practitioner*, 1957, **178**, 21.

Flying for the Elderly

Q.—*A woman, aged 78, with cerebral arteriosclerosis was mentally confused and subsequently amnesic on two out of several air journeys. One of these was in an unpressurized aircraft, which is believed to have flown substantially above 10,000 feet (3,048 m.). The other was in a "Viscount," which was pressurized. A diagnosis of temporary cerebral anoxia seems probable. Should she fly again?*

A.—A patient suffering from cerebral arteriosclerosis would show signs of hypoxia much earlier than a normal person. It is extremely unlikely that an unpressurized aircraft flew substantially above 10,000 feet (3,048 m.), since very few operators authorize such an altitude in such aircraft. It is also extremely unlikely that the cabin altitude of a Viscount was more than an equivalent of 8,000 feet (2,438 m.). In fact, such a cabin altitude would be found only at the very extreme height at which a Viscount can operate—i.e., around 30,000 feet (9,144 m.). Hysteria must not be discounted in the differential diagnosis, since some passengers exhibit symptoms of it. However, this patient's symptoms are extremely suggestive of hypoxia. She could fly again, but only in a pressurized aircraft, and with the additional provision of oxygen. Most reputable airlines provide this on application to their medical services.

Non-spermicidal Lubricant

Q.—*Can you suggest a non-spermicidal lubricant for use during coitus?*

A.—"K-Y jelly" or "prentif" surgical lubricant jelly are satisfactory non-spermicidal lubricants for use during coitus. Though non-spermicidal, a large volume of jelly in the vagina might offer some degree of obstruction to the motility of the sperm. Therefore it is preferable that the jelly be applied sparingly when conception is desired.

Assortment of Genes

Q.—*A patient is shortly getting married. She is an epileptic. One of her sisters is also epileptic and a congenital deaf mute, and another of her sisters is a deaf mute. This latter sister has two children, one of whom is a deaf mute and the other is normal. The patient has three brothers, two of whom are known to be suffering from mild haemophilia. Her mother is normal and her father was an alcoholic. I cannot elicit any more information about other members of the family. What is the risk of her producing abnormal children? The future husband has a normal family history.*

A.—Precise risks can be given only for the mild haemophilia. Assuming that the diagnosis of haemophilia in the brothers is correct, the patient has a 1-in-2 chance of being heterozygous for the sex-linked recessive gene concerned, and so there is a 1-in-4 risk of a son of hers developing haemophilia and of a daughter being a heterozygous carrier

of the gene. The risk of epilepsy in a child of a patient with epilepsy is about 3 to 4%,[1 2] but here, since the patient has a sister similarly affected, the risk is probably rather higher, but not a serious risk. The risk of deaf-mutism appearing in the children is difficult to assess. Most genetically determined forms of deaf-mutism appear to be due to one of a group of autosomal recessive genes.[3 4] These could be responsible here only if the deaf-mute sister who has a deaf-mute child has married a carrier of the same gene, and other genetic mechanisms might be concerned in this family. Nevertheless, the risk of deaf-mutism in the patient's children is probably not high. The main risk, therefore, is the 1-in-4 risk of haemophilia in the patient's sons.

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Obesity in Diabetes

Q.—*A man, aged 64, has had uncomplicated diabetes for 26 years. He has insulin three times a day. He has never dieted, and judges according to his appetite, but he is putting on weight. What should he do to maintain full activity and vigour and yet lose weight?*

A.—The control of diabetes by three daily injections of insulin and free diet might well prove satisfactory in respect of absence of complications, but is likely to lead to increase in weight. The solution of this problem is for the patient to adhere to a low-calorie diet and adjust the dosage of insulin accordingly. If the patient were to adopt this form of treatment it is probable that the diabetes could be satisfactorily controlled on two daily injections of insulin instead of three.

Ageing in the Tropics

Q.—*Does prolonged residence in tropical climates cause Europeans to age prematurely?*

A.—There is no evidence that prolonged residence in tropical climates causes premature ageing in any race. This is, of course, a field in which it is extremely difficult to collect accurate information, but one cannot fail to be impressed by the comparatively young appearance of many of those who have served long periods in the tropics. Provided routine hygienic precautions are observed, there is no reason to fear that the outlook will be adversely influenced either as regards ageing or as regards morbidity from a tropical environment.

Hypofibrinogenaemia and Obstetric Bleeding

Q.—*It is said that severe bleeding in childbirth may be foreseen and prevented if at the first sign of haemorrhage, even when clotting time is normal, the fibrinogen content of the blood is estimated. At what level should fibrinogen be given?*

A.—Only some bleeding in childbirth is due to a low blood fibrinogen level. Accidental haemorrhage is the commonest cause of hypofibrinogenaemia in pregnancy. Thromboplastin is then said to be released from the separated placental tissue and from damaged decidua into the maternal circulation, causing intravascular clotting with rapid depletion of the blood fibrinogen at a rate that the liver cannot replace sufficiently quickly. Less often hypofibrinogenaemia complicates other abnormalities of pregnancy such as prolonged retention *in utero* of a dead foetus and embolism of amniotic fluid.

In haemorrhage complicating childbirth hypofibrinogenaemia can be detected by simple direct observation of a sample of blood to see how long it takes to clot, or by any of a number of rapid tests, some of which, like the following, can be performed at the bedside.

To 0.2 ml. citrated blood in a small test-tube is added 0.2 ml. thrombin solution, freshly prepared by dissolving 50 N.I.H. units of dried thrombin in 1 ml. saline, both these being obtainable in ampoules. If the fibrinogen level is normal, clotting is evident in 5–10 seconds and the clot is firm and stable at 60 seconds. Delay of the initial clotting beyond 15–20 seconds and liquefaction or disintegration of most of the clot at 60 seconds shows considerable reduction of the fibrinogen level. Absence of clot formation within 60 seconds is evidence of afibrinogenaemia. A sample of blood from a normal person can be used as a control.[1]

Pure fibrinogen may be used to correct fibrinogen depletion but it is not readily available; 2–6 g. is given intravenously but serial tests and clinical observation may show that a smaller amount will suffice. The most practical procedure is to give by intravenous drip quadruple strength reconstituted dried plasma, a pint (570 ml.) of which contains about 4.4 g. fibrinogen. The doctor who practises obstetrics is advised to carry a giving set, dried plasma, and water for reconstituting it in one of his bags. Bleeding is very likely to occur, but is not inevitable, when the blood fibrinogen level falls below 120 mg./100 ml. The normal level in late pregnancy is 300–600 mg.%.

REFERENCE

1 *British Obstetric Practice*, 1959, edited by E. Holland, 2nd ed., pp. 801, 804. Heinemann, London.

NOTES AND COMMENTS

Blepharitis.—Mr. C. M. HEATH (Redruth, Cornwall) writes: Your expert (" Any Questions ? " January 30, p. 363) must indeed be living in the past if he ignores antibiotics in the treatment of ulcerative blepharitis; and I think that he will not be popular with those patients whom he disfigures unnecessarily by painting their eyelids violet with tinctorium. This was our only effective remedy 20 years ago against the severe chronic ulcerative blepharitis common among undernourished children, but this has now become much rarer and usually responds to antibiotics applied after bathing the lids clean with bicarbonate solution, although treatment may need to be persistent, changed at intervals, and sometimes combined with hydrocortisone. But your expert has not made it clear that now the common type is squamous blepharitis allied to dandruff and treated with bland remedies. A mild form often occurs with conjunctival engorgement from ocular fatigue and is then relieved by spectacles.

OUR EXPERT replies: Mr. Heath thinks it is old-fashioned to use tinctorium for blepharitis, but he proceeds to recommend sodium bicarbonate, a substance which many of us gave up prescribing for blepharitis years before tinctorium came into general use. Yes, I agree that some of the antibiotics are useful, but I think Mr. Heath looks for too much information in this question-and-answer medium. I was not writing a paper or an encyclopaedia article. My object was to give a simple and effective treatment for what has, in my experience, been the commonest type of blepharitis.

Correction.—In the " To-day's Drugs " comment on noscapine (*Journal*, December 26, 1959, p. 1481) the proportion of this in crude opium was said to be 16–22%. The correct figure should be about 2–9%.

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